~~Event related potentials in children with cochlear implants.~~

CORRELATION OF ELECTROPHYSIOLOGICAL MEASURES OF AUDITORY PROCESSING WITH OUTCOME IN PAEDIATRIC COCHLEAR IMPLANT PATIENTS.

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CONTENTS

FIGURES

TABLES

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ABSTRACT

OBJECTIVE:

Mismatch negativity (MMN) is a negative component in the human event related potential that occurs in response to a change in the nature of a repeating stimulus. Since it occurs even in the absence of attention, it reflects an automatic cerebral process for detecting change. The MMN is clinically helpful in detecting sensory memory and central processing deficits in groups, but its use as a clinical tool in individual patients is yet to be established. Late Discriminative Negativity (LDN) is another recently reported second negativity that follows MMN and has been suggested to reflect the automatic processing of complex linguistic stimuli in children.

The use of cochlear implants in profoundly deaf children is increasing with a trend towards earlier implantation. However the tools used at present to assess and predict outcome of cochlear implantation are primarily based on behavioural tests, which are difficult to use effectively in young children due to limitations in communication and cognitive skills in this age group. MMN has been proposed as a potential test which can be used to assess auditory memory and central auditory processing in cochlear implant patients.

The main objective of this study was to assess the correlation of auditory event related potential (ERP) measures with behavioural assessment data to identify if ERPs including mismatch negativity (MMN) can be used to categorize cochlear implant patients into good and poor performers.

DESIGN:

We carried out an observational, cross sectional, non-randomized, cohort study investigating auditory event related potentials to speech stimuli in 35 cochlear implant patients between the ages of 7 and 17 years and compared the occurrence, latencies and amplitudes of P1, N2, MMN and LDN with overall behavioural outcome in these children. Behavioural measures included category of auditory performance scores (CAP) and speech intelligibility rating scores (SIR).

RESULTS:

Auditory ERPs in response to standard stimuli were identifiable in 30 out of 35 patients, demonstrating a major positive component (P1) followed by a negativity (N2) with absence of N1 in all patients. The P1 component in pre-lingually deaf patients showed a statistically significant reduction in its latency with increasing duration of implant use. MMN was recorded in 80-85% of star performers but in only 15-20% of poor performers. Patients with higher SIR scores demonstrated statistically significant longer duration of MMN compared to those with a lower SIR score. Patients with higher SIR and CAP scores also demonstrated a statistically significant inverse relationship with the duration of LDN.

CONCLUSION:

These results indicate that MMN can be used to assess the functional status of the auditory cortex in young children with cochlear implants and may provide an objective mechanism for differentiating good from poor performers.

1 GENERAL INTRODUCTION

1.1 ANATOMY AND PHYSIOLOGY OF THE AUDITORY PATHWAYS

1.1.1 **Anatomy of peripheral auditory system**

The ear, which includes the peripheral auditory and vestibular apparatus, is divided into the external, middle and internal ear (Figure 1). The external ear consists of the auricle or pinna, and the external ear canal, at the medial end of which lies the tympanic membrane. The tympanic membrane separates the external ear from the middle ear. The middle ear or tympanic cavity is a small space in the temporal bone containing the auditory ossicles (malleus, incus, stapes) and air that communicates with the nasopharynx by the auditory tube (Eustachian tube).The medial wall of the middle ear adjoins the internal ear, which is composed of the osseous labyrinth, another space within the temporal bone, within which is the membranous labyrinth containing the auditory and vestibular sensory receptors (Anson & Donaldson, 1981).

The cavity of the osseous labyrinth is lined by endosteum and opens into the medial wall of the middle ear through the oval window covered by the footplate of the stapes and the round window covered by the secondary tympanic membrane. It also opens into the posterior cranial fossa through the aqueduct of the vestibule, which contains the endolymphatic duct, and the aqueduct of the cochlea, through which perilymph drains into the cerebrospinal fluid. The membranous labyrinth consists of one continuous closed cavity containing endolymph, which is lined by an outer vascular layer, an intermediate fibrous layer and an inner epithelial layer. The inner epithelium is further specialized into receptors of sound, static balance and kinetic balance and is supplied by the cochlear and vestibular divisions of the eighth nerve (Axelsson, 1968).

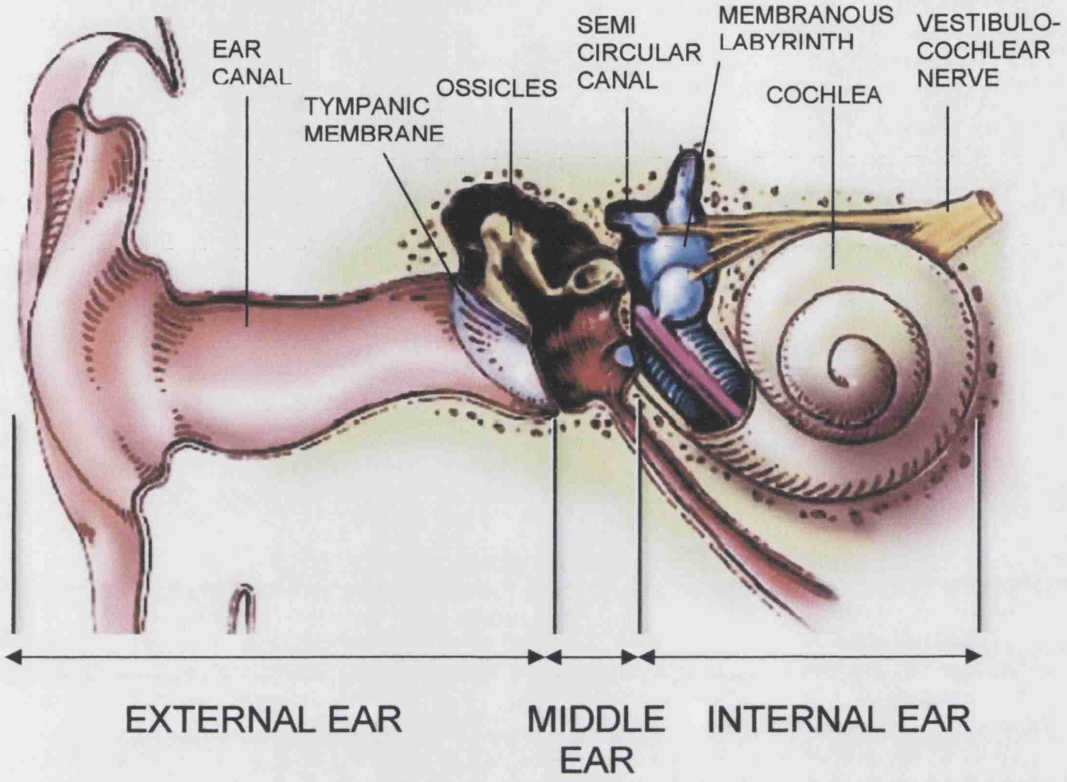

Figure 1: Gross anatomy of external, middle and internal ear.

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The cochlear duct is the spiral anterior part of the membranous labyrinth, which contains the sound receptors (See Figure 2A,B). Two membranes enclose the duct which is triangular in cross section. One side of the triangle is formed by the basilar membrane which extends in the line of the spiral lamina to the outer bony wall of the cochlea and throughout its length supports the spiral organ; another side is formed by the delicate vestibular (Reissner's) membrane. Connecting the two membranes and

completing the triangle, is the endosteum of the outer wall of the cochlea, which is thickened here to form the spiral ligament (Ota & Kimura, 1980).

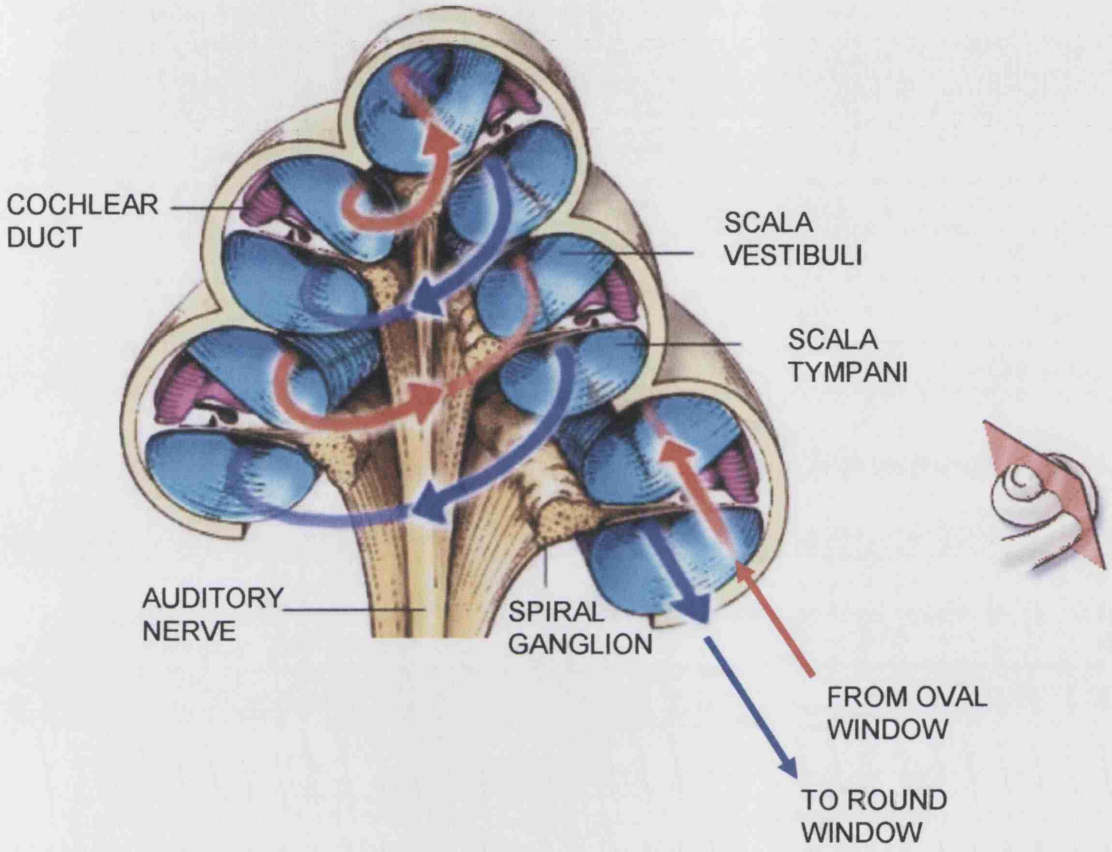

Figure 2A: Diagrammatic representation of the cross section of the whole cochlea

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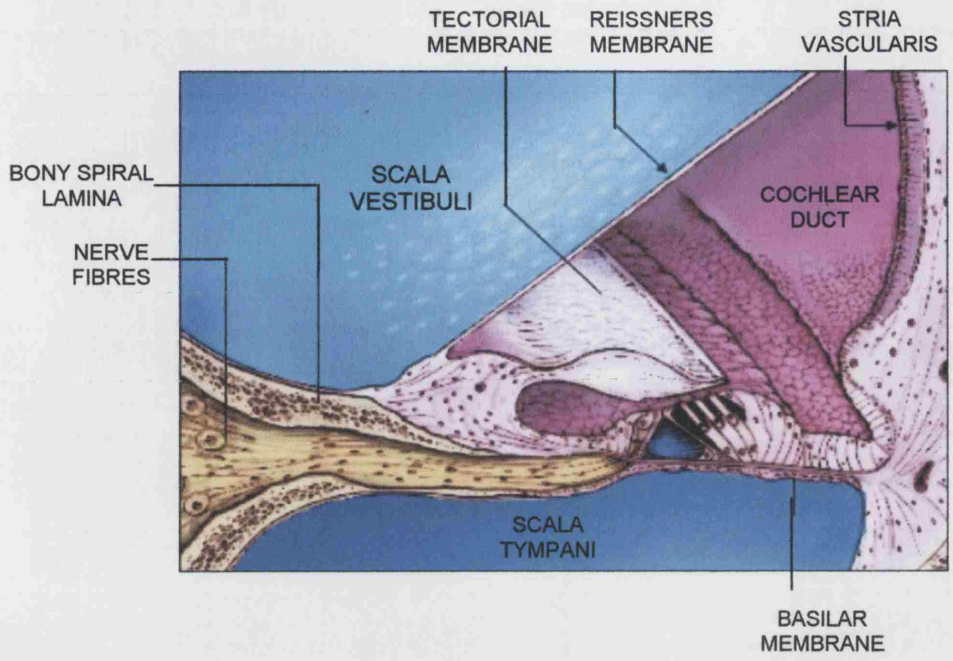

Figure 2B: Diagrammatic representation of the cross section of one single turn of cochlea

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In the spiral organ (of Corti) the sensory hair cells, the receptors for hearing are lodged on supporting cells. The hairs are modified microvilli (stereocilia) and are overlaid by the tectorial membrane, a sheet of keratin like protein that projects from beneath the inner attachment of the reissner's membrane. These hair cells are supported by the dendrites of the spiral ganglion (Bredberg, 1968).

The cells are called hair cells because they are characterised by having a cuticular plate with a tuft of stereocilia bathing in the surrounding endolymph. The cell body is localised in the perilymph compartment. Schematically, both types of cells, inner hair cells (IHCs) and outer hair cells (OHCs), differ by their shape and the pattern of their

stereocilia (Figures 3,4). In the human cochlea, there are 3,500 IHCs and about 13,000 OHCs (Bredberg, 1968). Like neurons, hair cells cannot proliferate after they are differentiated and the final number of hair cells is reached very early in development (around 10 weeks of foetal gestation) (Ashmore & Kolston, 1994; Ashmore, 1994).

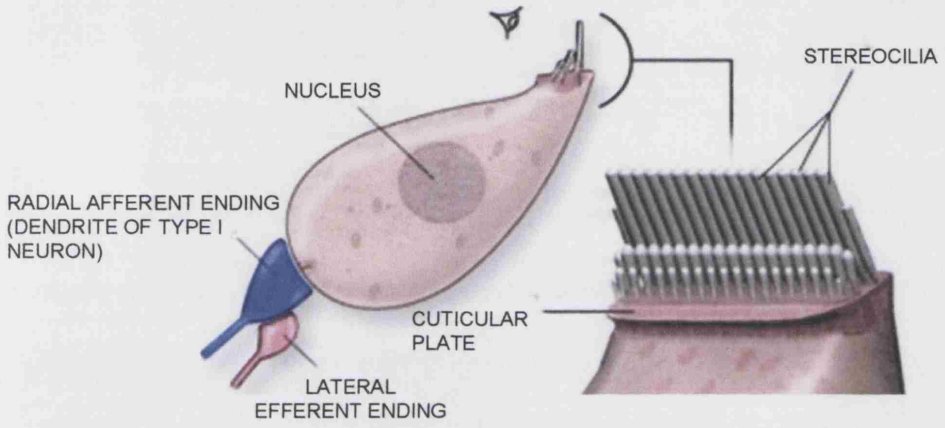

Figure 3: Inner hair cells

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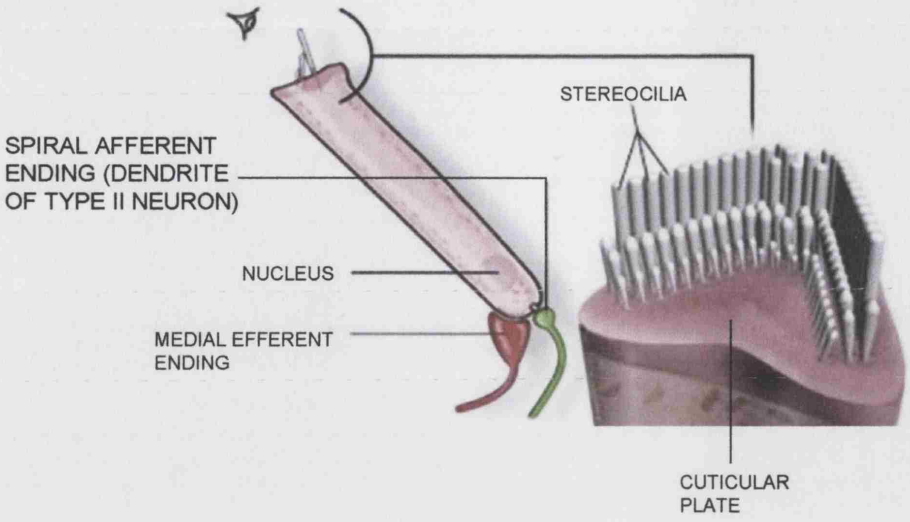

Figure 4: Outer hair cells

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1.1.2 **Physiology of peripheral auditory system**

Sound is the sensation produced when longitudinal vibration of molecules in the environment (alternate phases of condensation and rarefaction) strike the tympanic membrane. A plot of these movements as changes in pressure on the tympanic membrane per unit of time is a series of waves called sound waves. The waves travel through air at a speed of 344m/s at 20degrees Celsius at sea level, faster with increase in temperature and altitude. The loudness of a sound is correlated with the amplitude of the sound wave and its pitch with the frequency. Sound waves with repeating patterns are perceived as musical sounds while aperiodic non-repeating vibration cause a sensation of noise.

The ear converts external sound waves into action potentials in the auditory nerve. The sound waves are first transformed by the ear drum and auditory ossicles into movements of the footplate of the stapes. These movements set up waves in the fluid of the inner ear. The action of the waves on the organ of Corti generates action potentials in the nerve fibres.

The tympanic membrane functions as a resonator that reproduces the vibrations of the sound source. Its motions are imparted to the malleus which then transmits the vibration to the incus which in turn transmits the vibration to the head of the stapes. The auditory ossicles thus function as a lever system that converts the resonant vibrations of the tympanic membrane into movements of the stapes against the perilymph filled scala vestibule of the cochlea. This system increases the sound pressure that arrives at the tympanic membrane because the lever action of the ossicles multiplies the force 1.3 times and the area of the footplate is much smaller than the area of the tympanic membrane. The movement of the stapes set up a series of travelling waves in the perilymph of the scala vestibule. As the wave moves up the cochlea, its height increases to a maximum and then rapidly drops off. The distance from the stapes to this point of maximum height is dependent on the pitch of the sound. High pitched sounds generate waves that reach maximum height near the base of the cochlea whereas low pitched sounds reach a maximum height near the apex of the cochlea. The bony walls of the scala vestibuli are rigid but the Reissner's membrane and the basilar membrane are flexible. Movement of the stapes moves both these membranes and since they are hinged on different axis, this generates a shearing motion that deflects the hair cells. The process of signal transduction in hair cells has become clearer with recent advances in electrophysiology (Holton & Hudspeth, 1986). The individual stereocilia on the apical surface of the hair cells are rigid and

connected together with cross links. As a result they all move together as a stiff bundle. A travelling wave in the perilymph generated due to movement of stapes deflects this bundle causing the different rows of stereocilia to slide relative to one another. There are fine links that connect the tips of shorter stereocilia to the adjacent row of taller stereocilia. A deflection in the direction of the taller stereocilia stretches these links resulting in the opening of ion channels in the cell membrane ultimately leading to the generation of an action potential in the auditory nerve. A deflection in the opposite direction closes these channels. The inner hair cells are the primary sensory cells that generate action potentials in the auditory nerves, and presumably they are stimulated by the fluid movement as described above. The outer hair cells on the other hand are innervated by efferent fibres from the superior olivary complexes and there is evidence that these hair cells are motile. It appears that these hair cells improve hearing by influencing the vibration patterns of the basilar membrane (Pickles, 1985).

1.1.3 **Central auditory system:**

The cochlea is the primary receptor of the afferent auditory system and is modulated by the efferent auditory system. The afferent nerves, carrying sensory information to the brainstem, have their cell bodies in the spiral ganglion and their terminal dendrites make contact with the hair cells. The efferent nerves pass directly through the spiral ganglion, their cell bodies being located within the brainstem (See Figure 5). Each cochlear nerve in young normal individuals contains about 30,000 myelinated nerve fibres. These are virtually all afferent, as the efferent fibres travel initially in the superior vestibular nerve. The afferent fibres pass through the modiolus to the spiral canal where their cell bodies are found. 95% of the spiral ganglion cells are large,

bipolar and unmyelinated; the afferent fibres lose their myelin sheath a short distance before entering the cell body (Ota & Kimura, 1980). Each inner hair cell has about ten dendrites synapsing around the lower part of the cell body. The other 5% of spiral ganglion cells are small and may be myelinated or unmyelinated. Based on animal work, it is likely that the dendrites of these type 2 cells supply the outer hair cells (Pickles, 1985).

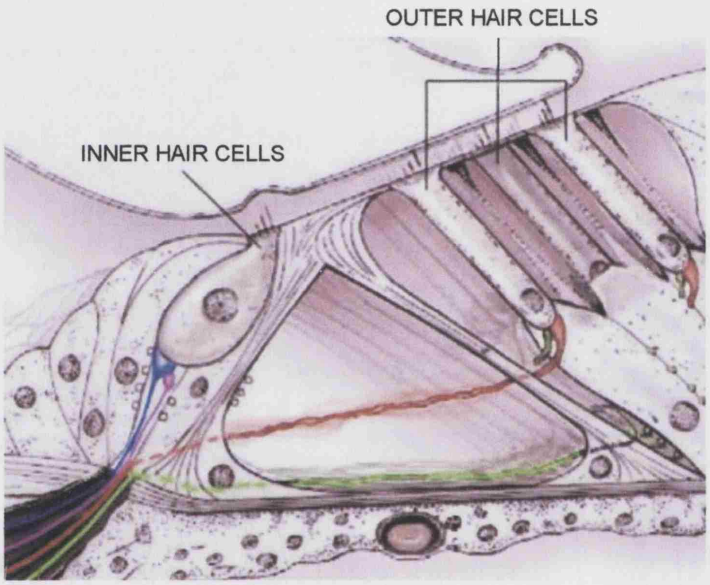

Figure 5: Innervation of inner and outer hair cells.

The radial afferents (blue) and the lateral efferents (pink) innervate the inner hair cells; the spiral afferents (green) and the medial efferents (red) innervate the outer hair cells.

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The efferent fibres with their cell bodies in the brainstem are few in number and arise in both the homo and contra lateral superior olivary complex. They travel initially in the superior vestibular nerve which they leave in the internal auditory meatus to join

the cochlear division by way of Oort's anastomosis. They enter the spiral canal within the modiolus and ascend or descend for a short distance. Some fibres subsequently supply the inner hair cells, while others run out across the tunnel of Corti to branch and terminate as large vesiculated nerve endings on several outer hair cells. The efferent innervation is most dense at the base of the cochlea gradually diminishing towards the apex (Spoendlin, 1984).

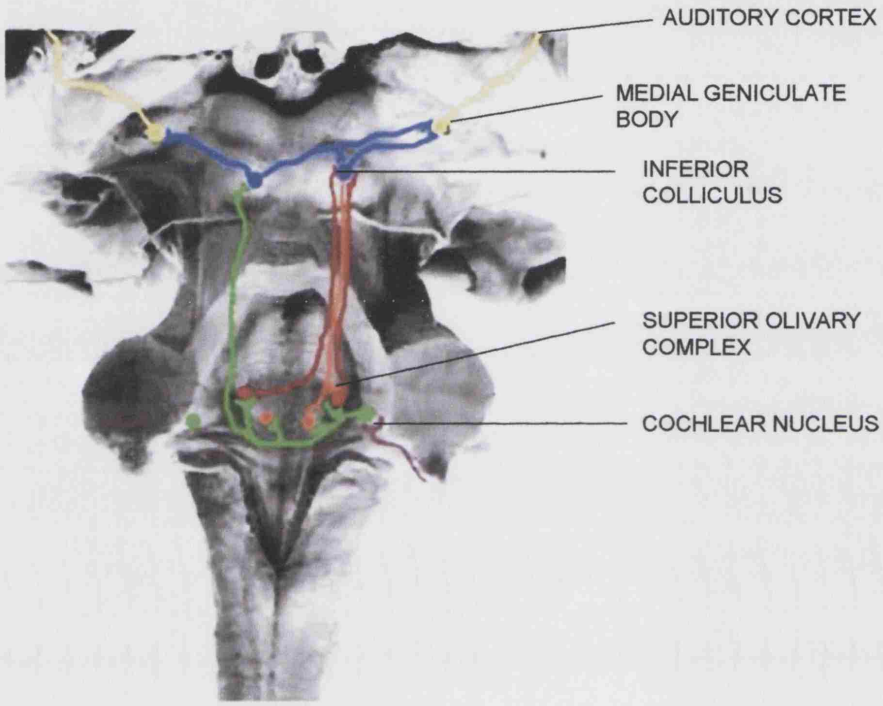


Figure 6: Diagram of CNS pathways for hearing.

Purple: cochlear nerve, green: second order fibres connecting cochlear nucleus to superior olivary complex, red: lateral lemniscus connecting superior olivary complex to inferior colliculus, blue: nerve fibres connecting inferior colliculus to medial geniculate body in the thalamus, yellow: fibres connecting thalamus to auditory cortex.

[With kind permission from Reyes S

(http://serous.med.buffalo.edu/hearing/auditory_nerve.html)

Afferent neurologic auditory pathways effectively begin with the first synapse at the cochlear nucleus (See Figure 6). The tonotopic organisation of the basilar membrane is continual throughout the cells and synapses of the afferent pathways. The afferent nerve fibres enter the brainstem at the level of the pons and terminate with second order neurons in one of the divisions of the cochlear nucleus. Some of the second order fibres cross the midline and either synapse with the superior olivary complex on the opposite side or bypass it to synapse with the inferior colliculus on the opposite side. The superior olives are the lowest level where information from one ear meets the other and are concerned with sound localisation. While some ipsilateral neuron synapses occur at the lateral lemniscus and the inferior colliculus, a large number of neurons from the cochlear nucleus extend contralaterally to the lateral lemniscus. Thus, there is bilateral representation to the inferior colliculus. From the inferior colliculus, the auditory pathways go ipsilaterally and contralaterally across the commissure of the inferior colliculus to the inferior colliculus and medial geniculate body on the opposite side. The medial geniculate body is the thalamic transfer region for the auditory system with primary projections to the auditory cortex originating in its ventral division. It is hypothesised that the auditory neurologic pathway structure is one of an ascending and descending parallel system with the efferent system providing a control of the afferent transmission originating at the cochlea (Rubel & Dobie, 1989).

1.1.3.1 Primary and non-primary auditory pathways

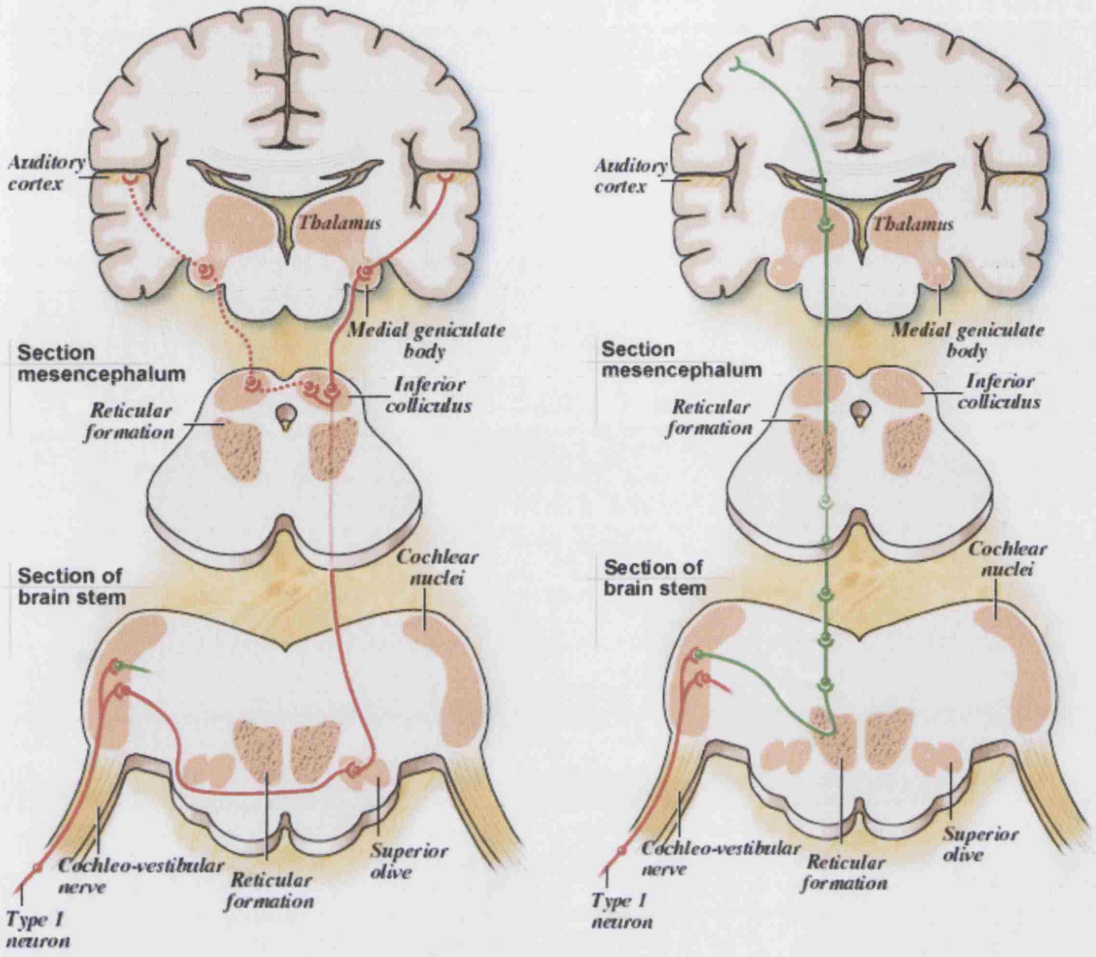
Auditory activity is conveyed to the brain via two types of pathway: the primary auditory pathway which exclusively carries information from the cochlea, and the non-primary pathway (reticular sensory pathway) that is multisensory (Figure 7).

1.1.3.1.1 *Primary auditory pathways:*

Schematically, this pathway has 3 to 4 relays, contains large myelinated fibres, and ends in the primary auditory cortex. The pathway carries information from the cochlea, and each relay nucleus does a specific task of decoding and integration.

1.1.3.1.2 *Non-primary pathways:*

From the cochlear nuclei, small fibres connect with the reticular formation where the auditory message joins all other sensory messages. The next relay is in the non-specific thalamus nuclei before the pathway ends in the polysensory (associative) cortex. The main function of these pathways, also connected to wake and motivation centers, and vegetative and hormonal systems, is to select the type of sensory message to be treated first. For example, when reading a book and listening to music at the same time, this system allows the person to pay attention alternately to the more important task.



PRIMARY AUDITORY PATHWAY

NON PRIMARY / RETICULAR AUDITORY PATHWAY

Figure 7: Diagram to illustrate primary and reticular auditory pathways

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Conscious perception requires the integrity of both types of pathways. For instance, during sleep the primary auditory pathway functions normally, but no conscious perception is possible because the link between reticular pathways and the wake and motivation centres is inactive. Conversely, trauma affecting the cortex may suppress conscious perception, while the continuing integrity of the non-primary pathways may result in vegetative reflex reactions to a sound (Syka & Aitkin, 1988).

1.1.3.2 Auditory cortex

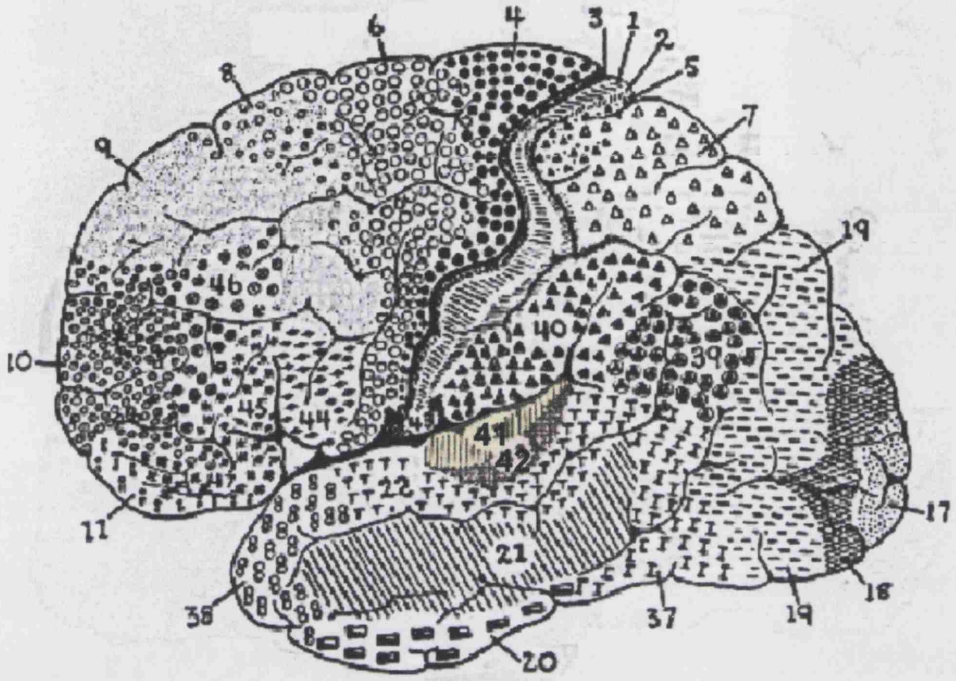

Figure 8: Brodmann architectural map. Note areas 41 and 42 that correspond to AI and AII respectively. (After Liasis 2000)

The auditory reception area of the cortex has been shown to occupy the transverse portion of Heschl's gyrus in the superior temporal lobe and insula, known as the primary auditory cortical area (A1). The second important auditory area (A2) is located anterior to A1 and continues the tonotopic organisation initially seen in the cochlea. A1 and A2 are also known as Brodmann's areas (BA) 41 and 42 (See Figure 8). The posterior inferior frontal lobe and inferior parietal lobe have also been shown to be associated with auditory response.

It is hypothesised that there may be two ways in which information is organised within A1. Firstly, like other areas of the cerebral cortex, A1 is organised in functional columns. All neurones encountered in a vertical microelectrode penetration

of A1 respond optimally to sound in the same frequency range (Barlow & Mollon, 1982). Secondly, like the cochlea, A1 is organised tonotopically: more anterior regions of the auditory cortex are responsive to higher frequencies, and posterior regions are responsive to lower frequencies.

1.1.4 **Auditory deprivation and neural plasticity**

Auditory experience plays a very important role in laying down the fine organizational structure of the auditory pathway onto an underlying framework generated by genetic cues. Although lack of auditory experience in congenitally deaf children leads to development of a more rudimentary auditory pathway, this reduced level of organisation is still sufficient to provide both temporal and spatial cues necessary for speech perception via a cochlear implant (Shepherd & Hardie, 2001).

A profound sensorineural hearing loss induces significant pathological and atrophic changes in the cochlea and central auditory pathways. A comprehensive review of experimental work in this field has been detailed by Shepherd and Hardie in 2001. A summary of the main morphological changes due to sensorineural hearing loss is detailed below:

- Ongoing degeneration of spiral ganglion cells
- Atrophic changes within the central auditory pathway including reduction in soma area and nuclear volume
- No loss of central neurons if hearing loss occurs after the onset of hearing.
- Changes in synaptic architecture and evidence of loss of synapses and synaptogenesis.

- Decreased inhibitory influences and altered metabolic status of central auditory neurons.

The main functional changes due to a sensorineural hearing loss can be summarised as below:

- Partially degenerated spiral ganglion cells remain capable of generating and propagating action potentials via a cochlear implant.
- The central auditory pathway can be readily activated following many years of deafness.
- The basic neural responses to an electrical stimulus remain unaffected following a long term sensorineural hearing loss.
- Functional neural connections along the central auditory pathway are established with minimal auditory experience.
- The central auditory pathway exhibits a rudimentary cochleotopic organisation even in the absence of extensive auditory experience.
- Reduction in the temporal resolutions of auditory nerve fibres and central auditory neurons.
- Significant increases in response latency of central auditory neurons.

Brain plasticity is described as the competition of sensory afferents for cortical space. When occurring very early in life, sensory deprivation leads to recruitment of deprived cortices by inputs from intact senses (Bavelier, Tomann et al., 2000; Weeks, Horwitz et al., 2000). Therefore in pre-lingually deafened subjects, auditory cortex has been shown to participate in processing sign language (Nishimura, Hashikawa et al., 1999; Nishimura, Doi et al., 2000a; Nishimura, Doi et al., 2000b). Cortical

plasticity resulting from deafness generally spares primary auditory regions but affects post processing cortices. However the degree and nature of reorganisation in secondary and association auditory cortices is variable depending on whether deafness occurred before or after critical stages in language development. In pre-lingual deaf subjects, hard wired cross modal connections limit participation of these regions in oral communication. In contrast, in post-lingual deaf patients, cross modal compensation is less significant and involves mechanisms which are reversible and therefore permit full functional recovery (Giraud, Truy et al., 2001; Giraud, Price. et al., 2001).

Brain plasticity continues to occur after cochlear implantation. Similar to changes due to deafness, the most important time related changes are not observed in the primary auditory cortex, but instead in auditory association cortices. Repeated use of any given cognitive strategy induces further cortical plasticity. Completing and complimenting the information provided by an implant by cues gathered from other sensory modalities such as vision is a common strategy that progressively gives rise to stable complimentary cross modal effects. The dynamics of these cross modal effects suggest that restoration of auditory inputs by a cochlear implant results in mutual reinforcement of vision and hearing rather than return to segregation between the senses (Giraud, Truy et al., 2001).

1.2 COCHLEAR IMPLANTATION

1.2.1 **Introduction to cochlear implants:**

Cochlear implant is a prosthetic device, which can be implanted in the inner ear and can restore partial hearing to profoundly deaf people. Several cochlear implant devices have been developed over the years.

The main features of a cochlear implant are (See Figure 9):

1. a microphone that picks up the sound,

2. a speech processor that converts the sound into electrical signals,

3. a transmission system that transmits the electrical signals to the implanted electrodes, and

4. an electrode array (consisting of multiple electrodes).

The electrode array is inserted into the cochlea by a surgeon. In contrast to a single electrode, the array permits different nerve fibres to be stimulated at different places in the cochlea, exploiting the place mechanism for coding frequencies in the cochlea. Different electrodes are stimulated depending on the frequency of the signal. Electrodes near the base of the cochlea are stimulated with high frequency signals, while electrodes near the apex are stimulated with low frequency signals. The speech processor, much like a healthy cochlea decomposes the input signal into its frequency components and delivers these signals to the appropriate electrodes in the implanted package. The speech processor also controls the amplitude of the stimulus current delivered to the electrode which depends on the loudness of sound being processed.

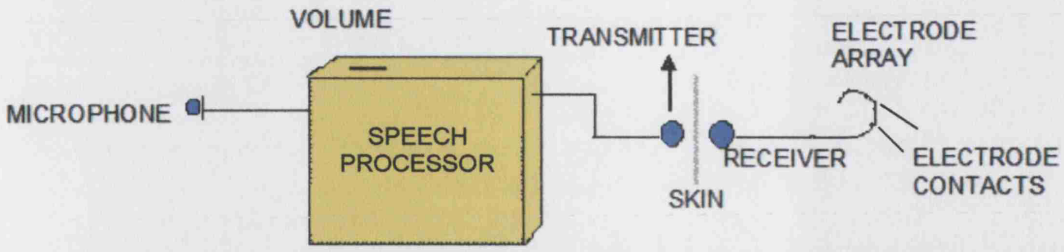

Figure 9: Schematic representation of a cochlear implant

In summary, the implant can effectively transmit information to the brain about the loudness of the sound, which is a function of the amplitude of the stimulus current, and the pitch, which is a function of the place in the cochlea being stimulated.

1.2.2 **Criterion for implantation**

The main criteria that need to be met for cochlear implantation are as follows (Lenarz, 1998; Eisenberg, Martinez et al., 2000) The hearing loss has to be severe (pure tone average threshold greater than 70dB HL) or profound (pure tone average threshold greater than 90dB HL) and it has to be bilateral.

1. The candidate's sentence recognition scores should be less than 30% correct, under best aided conditions. The person must gain little or no benefit from the use of hearing aids.

2. The person should be 12 months of age or older at the time of surgery. However assessment of suitability for an implant can begin at younger ages.

3. Ideally the person should have developed verbal or pre-verbal communication skills. In those candidates who have enjoyed auditory input in the past, it is

important to establish whether auditory input contributed to the development of their communication skills.

4. The ears must be free of infection.

5. The auditory nerve must be intact.

6. The person must be medically suitable to undergo an operation under general anaesthesia.

7. The person must be motivated to use the device. Adjusting to the new sound provided by the cochlear implant device can take many months and can often be frustrating. Candidates and their families need to be prepared to persevere and practice to improve their listening and communication skills.

8. The person and their families must have realistic expectations of the device. Before a candidate decides to proceed with surgery, they should be aware of the limitations of the device.

1.2.3 **Assessment of cochlear implant candidates**:

A detailed assessment is carried out to ascertain if cochlear implantation is the right decision for rehabilitation of a deaf child. This is carried out by the audiological physician, ENT surgeon, teacher of the deaf, audiologist, audiological scientist, speech and language therapist and clinical psychologist. The assessment is in two stages.

1.2.3.1 First stage:

The child's hearing is assessed in detail. Hearing thresholds across all frequencies are established using pure tone and impedance audiometry. It is important to ensure that every child has had the best possible hearing aids and ear moulds and has used them consistently before proceeding with decisions about cochlear implantation. This is assessed based on reports from parents and assessments carried out by the child's teachers and local therapists.

1.2.3.2 Second stage:

Detailed assessment is carried out at home and schools by the cochlear implant team members namely the teachers of the deaf, speech and language therapists and clinical psychologists. This includes assessments of language, communication, education and expectations.

Radiological investigations including CT scan and MRI are carried out to assess the anatomical integrity of the cochlea, cochlear nerve and surrounding soft tissues. Auditory brain stem responses are recorded at this stage to objectively assess the threshold of hearing in both ears.

Findings of all the above investigations and detailed assessment reports prepared by the members of the cochlear implant team are discussed in a team meeting where the decision to implant the child or not is taken.

1.2.4 **Electrophysiological and objective measures:**

Electrophysiological tests have a very valuable role to play in the assessment and management of cochlear implant patients especially the young complex cases and those patients who are otherwise difficult to test. They are used in:

- Assessment of level of hearing loss
- Guidance in the selection of ear and patient for implantation
- Monitoring the functioning of the implant and identification of possible faults
- Assistance with the tuning of the device

1.2.4.1 Before implantation:

Brain stem evoked response audiometry and Electrocochleography are used to confirm the diagnosis of profound hearing loss and support the results of behavioural audiological assessment. In those patients where there is any doubt about the status of the auditory nerve, responses can be evoked using electrical stimulation presented at the promontory or round window in the middle ear (Nikolopoulos, Mason et al., 2000) . The evoked potentials thus evoked are the electrical auditory brainstem responses (EABR). These potentials confirm that the auditory nerve is intact and transmitting actively into the brainstem (Garnham, Cope et al., 2000; Mason, Sheppard et al., 1993).

1.2.4.2 After implantation:

The following electrophysiological and objective measures can be performed using the cochlear implant during and after implantation (Kileny, Zwolan et al., 1994; Mason, O'Donoghue et al., 1997):

1. Electrical stapedius reflex (ESR)
2. Neural response telemetry (NRT)
3. Electrically evoked sensory potentials (e.g. EABR)
4. Electrode impedance telemetry (EIT)
5. Integrity testing (IT)
6. Electrically evoked event related potential (EERP) – MMN, P 300, N1, P1, N2

Thresholds of the electrical auditory brainstem response (EABR) and neural response telemetry (NRT) are used to assess appropriate threshold levels of electrical stimulation for the tuning map. The thresholds of Electrical Stapedius Reflex (ESR) are used to assess the highest comfortable levels (dynamic range) for the patient.

The neural response telemetry (NRT) is a recent development that enables electrically evoked action potentials to be recorded from within the cochlea. The newer generation of Cochlear Implants is equipped with this facility. This is achieved by a reverse telemetry system that is incorporated in the design. Reverse telemetry works by sampling and digitising the voltage generated on the internal electrodes during stimulation by a computer interface. This information is then sent back to the

programming software thus enabling assessment of the functioning of the internal device.

The evoked action potential is a peripheral measure of nervous system activity and is a direct assessment of the auditory nerve response. It is independent of subject state and age and has the following main advantages:

1. Since the recording electrode for the EAP is generally located in or near the cochlea, the response amplitudes are larger than EABR or EMLR measures. As a result, the signal to noise ratio is more favourable requiring fewer sweeps in the averaging process.

2. The multi-electrode array of recording electrodes allows assessment of spread of excitation in the cochlea. In contrast, scalp electrodes cannot take advantage of the spatial response properties as in the EAP (Abbas & Brown, 2000).

The techniques of EIT and IT can be used to identify faults with the implant and the electrode array. Most implant centres apply at least one or more of these tests at the time of implant surgery with the following aims:

1. Immediate reassurance to the surgeon, adult patients and parents of implanted children that the implanted receiver and electrode array are functioning normally and that the auditory nerve is being stimulated.

2. To provide valuable information to assist the initial fitting and tuning of the implant, particularly in young children and complex cases.

3. Establish a reference set of data to assist with subsequent management.

4. After implantation these tests are valuable tools for the identification and management of electrode faults, device failure and difficulties with tuning. In particular IT is an essential tool for monitoring functioning of the device in children who were implanted a few years ago when the technique of EIT was not available.

1.2.5 **Surgical procedure / complications:**

The main aim of the surgical procedure is to anchor the receiver-stimulator package in the temporal bone in the skull and to insert the electrode array into the cochlea. This is done by first raising the skin from the skull behind the ear to expose the temporal bone. The surgeon is then able to position the implant package flat against the bone. Next, a cortical mastoidectomy followed by a posterior tympanotomy is performed to allow access to the cochlea. This is followed by establishing access to the scala tympani either indirectly by cochleostomy which involves drilling a hole in the wall of the cochlea at the promontory, or directly through the round window membrane. This allows the electrode array to be gently guided into the shell-like cochlea. The implant package and array is next fixed in place, and the wound is closed. The cochlear implant procedure typically takes 2 to 3 hours to complete. The hospital stay is normally 3 or 4 days. In experienced hands, serious complications are quite rare (Johnson, Gibbin et al., 1997). The potential surgical complications are wound infection, facial nerve palsy and meningitis (Daspit, 1991).

Surgery in children does not differ substantially from that in adults since the inner and middle ears are well developed and adult size at birth and the facial recess is also fully developed in neonates (Dahm, Shepherd et al., 1993). The surgeon however has to

accommodate for the relatively larger size of the receiver stimulator portion of the internal device to a thinner scalp and calvarium.

1.2.6 **Assessment of progress after cochlear implantation**

All cochlear implant programmes develop and maintain a sensitive assessment battery not only to assess benefit from the implant but also to monitor tuning and functioning of the device and to evaluate the effectiveness of the rehabilitation programme (Boothroyd, A., 1991) especially in the light of increasing evidence of intermittent hardware faults which can be difficult to identify in young children with minimal language who are unable to describe what they hear (Tyler & Kelsay, 1990). In addition, accurate assessment also enables comparison between different devices available.

Assessment of the benefit received by children with cochlear implants has primarily been based on measuring changes in speech perception and production after implantation (Osberger, Robbins et al., 1991a; Osberger, Maso et al., 1993; Staller, Dowell et al., 1991). However the 2 – 4 year olds, who are the most rapidly growing group of cochlear implantees, have very little spoken language or communication skills. In order to carry out any meaningful assessment, it is important that the tests are within the language and vocabulary capabilities of the child, their cognitive and motor abilities and attention span (Boothroyd, 1991). These considerations have necessitated the development of observational and proxy techniques that do not place a heavy linguistic load on the child.

Audiological assessment of the child's ability to detect sound using the cochlear implant package is carried out using sound field warble tone threshold testing across the speech frequency range. Although the sound field threshold is merely a reflection

of the sensitivity of the microphone and input circuitry of the processor, it has two other important uses. Firstly, it provides a clear demonstration to parents and local professionals about the lowest sound levels detectable by the child and secondly it provides a baseline for a quick check confirming the device is functioning well.

Further audiological assessment is employed to assess the ability of the child to discriminate words, especially without lip reading. This is performed using the McCormick automated toy discrimination test (Ousey, Sheppard et al., 1989). This test presents digitally stored word tokens at precisely calibrated levels to obtain the threshold level for correct identification with a standard adaptive algorithm. The child simply points to the toy corresponding to the word token. As such, no spoken response is necessary. Results of these tests indicate the child's speech perceptual ability. The threshold indicates auditory sensitivity and the ability of the child to organize incoming acoustical information into a meaningful word.

Communication skills are assessed by a combination of observation of the child (video analysis) and questionnaire / interviews of parents and local professionals.

The Listening Progress (LiP) Profile has been developed by the Nottingham cochlear implant programme to assist in monitoring early listening skills (Archbold, 1994). It is particularly helpful in monitoring progress in children with little or no language. It does not place the child in a test situation but gathers information by proxy about the child's developing listening abilities within the normal rehabilitation settings at home and in school. LiP covers the early stages of detection, discrimination and first stages of identification of sounds.

Video analysis also helps in monitoring early communication skills (Tait, 1993). A short video is usually recorded before implantation and at regular intervals after

implantation. In each of these sessions, the child interacts with a speaker well known to him / her. Precursors of normal language development such as eye contact with the speaker and turn taking, which is normally poor in deaf children, can be assessed using video analysis. One can also assess the amount of autonomy the child is showing during these tests. Examples of autonomy could include contradicting the adult, joking or asking questions. Auditory processing can also be assessed in video analysis. One of the clearest indications of auditory processing is that the child begins to take vocal turns after breaking eye contact with the adult. These can also be quantified by counting the number of times the child does this in a single recording session.

The profile of actual speech skills (PASS) is a video time sampling procedure. It was originally developed by the Indianapolis cochlear implant programme (Osberger, Robbins et al., 1991a). Initial utterances are assigned to one of four categories: 1) actual phonemes, 2) speech like sounds, 3) non-speech vocalizations and 4) silent speech postures. In addition, consonant and vowel systems, place of articulation and voice and manner features are also assessed. PASS has proven to be very useful in the assessment of children who do not have any language capabilities and are therefore unable to perform any formal speech test.

The test for reception of grammar (TROG) is a multiple choice test of language comprehension which consists of 80 four choice items. The test is appropriate for a wide range of 4-12 year olds.

The Speech Intelligibility Rating (SIR) is used to monitor the developing intelligibility of speech and voice. The Category of auditory performance (CAP) is also used to rate the outcome of cochlear implantation in everyday life. (See section

3.3.6) Results obtained from cochlear implant patients clearly demonstrate the development through these categories during post-implant assessments at regular intervals.

The Meaningful Auditory Integration scale (MAIS) is a questionnaire based assessment originally developed in Indianapolis in 1990 (Robbins, 1990). All parents and teachers receive the questionnaire and are asked to score the child regularly, responding to questions about the child's wearing of the device, awareness of environmental sounds and the ability to deduce subtle meanings from sounds such as distinguishing one speaker from another.

For the child's safety, awareness of environmental sounds is a very important objective of implantation for many parents. Parents are asked to comment on their child's responses to a range of 50 common environmental sounds and the increasing ability to identify these sounds.

Further information about the child's progress is collected through regular structured interviews. These allow parents more freedom to elaborate on their observations than is possible when completing a questionnaire. The probing investigates communication skills, spoken language, listening skills and behaviour.

1.2.7 **Outcomes**

A number of studies have established the effectiveness of cochlear implants in providing improved auditory function to deaf (severe to profound) patients (Osberger, Robbins et al., 1991b). Although a cochlear implant does not return a persons hearing completely to normal, the actual percept is a true hearing percept similar to what is

experienced with hearing aids or when the patient had normal hearing (Knutson, Murray et al., 1998).

Speech perception scores collected from children with cochlear implants suggests that children with a hearing loss in the profound range enjoy greater speech perception benefits from a cochlear implant than they do from their hearing aids. Although even in the hearing aid group, the speech perception skills improve over time, they do not keep pace with the gains achieved by children who receive a cochlear implant (Meyer, Svirsky, et al., 1998). After cochlear implantation, congenitally deaf children progressively improve in their speech perception abilities. Although the ability to speak without lip reading is limited in the first two years after implantation, significant improvement continues until 6 years. It can however take much longer for a child to use a cochlear implant effectively in everyday conversational speech (Nikolopoulos, Archbold et al., 1999; O'Donoghue, Nikolopoulos et al., 1998).

A meta-analysis of paediatric cochlear implant literature has shown that open set speech understanding is seen in over half the reported implanted children within two years of implantation. This paper also suggests that not only is earlier implantation associated with increased gains in speech recognition, speech perception benefits never plateau with time. It further points out that differences in performance between congenital and acquired causes of deafness diminish over time (Cheng, Grant et al., 1999).

The outcome of paediatric cochlear implantation is very widely variable. Young pre-lingually deaf children exhibit great variation in their auditory, cognitive and linguistic maturity which is very difficult to quantify. For example, there are no reliable measures that can be used to assess central processing mechanisms that are

crucial for recognition of speech presented using a cochlear implant. Numerous studies have been carried out to explore the variability in the outcome of paediatric cochlear implantation. They have confirmed that the most important known determinants of speech perception in young cochlear implanted children is the age of implantation and communication mode (Hodges, Dolan et al., 1999; Meyer, Svirsky, et al., 1998; O'Donoghue, Nikolopoulos et al., 2000). Age at implantation was found to be a strong negative predictor of speech perception and speech intelligibility in congenitally deaf children (Nikolopoulos, O'Donoghue et al., 1999). Children who use an oral mode of communication have significantly better spoken word recognition and receptive and expressive language abilities compared to children who use total communication (Miyamoto, Kirk et al., 1999).

A number of studies have shown that restoration of input by electrical stimulation of the auditory nerve using a cochlear implant can partially reverse the effects of auditory deprivation (Hyson & Rubel, 1989; Matsushima, Shepherd et al., 1991; Webster, 1988). Improvement with auditory experience suggests that neural plasticity and functional reorganization within the central auditory pathways may be the main reasons for improvements in clinical performance (Nikolopoulos, Archbold et al., 1999; O'Donoghue, Nikolopoulos et al., 1998). Other studies in long term pre-lingually deaf adults (Lee, Lee et al., 2001; O'Donoghue, Nikolopoulos et al., 1998) have demonstrated that the auditory cortex can get permanently routed to other cognitive processes such as visual processing in those using sign language or lip reading.

In comparison to children using hearing aids, cochlear implant recipients are significantly better in the finer aspects of speech that contribute to speech

intelligibility such as the natural variation in tones and volume and clearer endings of words which signal plural and past tense. This may be because they are able to use the auditory feedback provided by the implant system to improve control of the nasal oral balance of their speech (Svirsky, Jones et al., 1998). At 4 years post-implant, a significant correlation was found between speech perception and speech production. At 5 years, the median speech intelligibility was 'intelligible to a listener with little experience of deaf speech (Allen, Nikolopoulos et al., 1998).'

Cochlear implantation accompanied by aural rehabilitation improves the verbal and educational independence of children with profound deafness. This was concluded on the basis of classroom placement and number of hours of special education support used. Children with more than two years of implant experience were placed in a mainstream school at twice the rate or more of age matched children with profound hearing loss who did not have implants. They were placed much less frequently in a classroom especially for deaf students and used fewer hours of special education support (Francis, Koch et al., 1999). It has been shown that the rate of improvement in speech perception ability is significantly higher in those paediatric cochlear implant recipients who move towards or remain in the mainstream environment (Daya, Ashley et al., 2000).

Good speech perception is one of the most important outcomes of cochlear implantation. However it is not the only one. Other benefits such as relief from auditory isolation, help with lip reading, and awareness of warning sounds can make major contributions to a child's quality of life even if speech perception remains poor. Further, although age at implantation and mode of communication are important

factors that decide the outcome of implantation, other factors yet to be identified might also have a bearing on outcome (O'Donoghue, Nikolopoulos et al., 2000).

1.3 INVESTIGATION OF CENTRAL AUDITORY FUNCTION

Investigation of central auditory function requires a multidisciplinary approach with careful consideration of cognitive, memory and linguistic parameters. The diagnosis of central auditory dysfunction relies on:

- History of the patient (medical, educational and psychological / cognitive development),
- Baseline audiometric tests

  pure tone audiogram, tympanogram, oto-acoustic emissions
- Behavioural tests,

  mono-aural low redundancy tests (filtered words, auditory figure-ground test), dichotic tests / binaural interaction tests (dichotic digits, competing sentences), temporal tests (frequency pattern test, temporal gap detection)
- Electrophysiological tests,

  auditory brain stem evoked response, middle latency response, P 300, mismatch negativity.
- Speech and language assessment
- Psychological / cognitive assessment and
- Neuroimaging,

Behavioural tests have the advantage of being relatively easy and inexpensive to administer in experienced hands. However the main disadvantage is that results of behavioural tests may be easily confounded by extraneous variables such as age of the patient, motivation, extent of peripheral hearing loss, motor skills, native language, response strategies, visual acuity, cognitive demands (memory and attention), learning and/or practise effects and linguistic demands. Electrophysiologic and electroacoustic tests have the advantage of being influenced less by extraneous variables. The disadvantage however is that they are more time consuming and expensive to set up. Also facilities for such testing are not widely available. Many behavioural test paradigms can be incorporated within electrophysiologic procedures, thus providing both performance measures and gross site specific information from the same test session.

A number of methodologies allowing non-invasive evaluation of brain function and organisation have made it possible to investigate central auditory function in the human central nervous system. These are: electroencephalography (EEG) (Ponton, Eggermont et al., 2000a), magnetoencephalography (MEG) (Hari, 1997), magnetic resonance imaging (MRI), functional MRI (fMRI) (Ogawa, Menon et al., 1993) and positron emission tomography (PET) scans (Johnsrude, Giraud et al., 2002). MRI has the distinct advantage over most other methods of a high spatial resolution (millimetres), while scalp recorded evoked potentials, are known for their high temporal resolution (milliseconds), with the spatial resolution of the technique being limited by the inter-electrode distance and distance from source of activity i.e. cortex to scalp spread (Jerger & Musiek, 2000).

MEG measures the magnetic fields generated by electrical activity within the brain, as opposed to EEG techniques, which detect the brains' electrical activity. The magnetic fields recorded by MEG techniques are very small and recordings are carried out in magnetically shielded rooms and measured using super-conducting quantum interference devices which operate optimally at a temperature of -269 degrees and therefore have to be cooled using liquid helium. A relatively newer technique is functional MRI (fMRI) that exploits a phenomenon known as the BOLD (blood oxygen level dependant) effect to identify regions of the brain that are involved in performing specific tasks (Ogawa, Menon et al., 1993). fMRI is non-invasive and if optimised provides images of brain activity with a spatial resolution of less than 2 mm and a temporal resolution in the sub second stage. This technique can be used for pre-surgical assessment of auditory pathways functionality up to the primary auditory cortex (Berthezene, Truy et al., 1997). These assessments can be carried out using non-magnetic electrodes applied either transtympanically to the promontory or into the external auditory meatus (Hofmann, Preibisch et al., 1999). Conventional cochlear implants are not compatible with fMRIs. This is due to problems relating to high magnetic fields which can damage electronic elements located within the skull and artefacts induced by magnetisable elements. Although MRI compatible implants are now being manufactured, recent studies have indicated that even with such implants, MRI should only be used for medical indications (Teissl, Kremser et al., 1999). In a recent paper, Lazeyras and co-workers have recorded fMRI images in a patient using a cochlear implant (Lazeyras, Boex et al., 2002). Results of their work revealed bilateral localized activation of the primary auditory cortex. Stimulation of two different intracochlear electrodes elicited activity in two neighbouring, but different regions in agreement with the known tonotopical organization of the auditory cortex.

Their work has paved the way for future fMRI studies using a broad selection of auditory paradigms. Although inferior to fMRI in terms of temporospatial resolution, the most commonly used techniques for functional imaging in implant patients are positron emission tomography (PET). Functional PET relies on radio-labelled water ($H_2{}^{15}0$) which when injected into the body crosses the blood brain barrier and collects in regionally active cortical areas. This technique is safe for patients and implants and compatible with implant function during data acquisition and has been the technique of choice for studying plasticity in implant patients (Section 1.1.4).

The above described tests lack the ability to differentiate an auditory specific disorder from other disorders that may impact auditory processing. This can be achieved by carrying out analogous behavioural and/or electrophysiologic test procedures in a non-auditory modality like vision. One possible approach is to compare behavioural performance scores on comparable auditory and visual continuous performance measures. For example duration patterns of long and short light flashes can be compared with analogous duration pattern of long and short noise bursts. Another similar example would be to study the P300 / MMN event related potential, using analogous auditory and visual temporal processing tasks in order to confirm whether a deficit is present in both modalities or is limited to the auditory modality (Jerger & Musiek, 2000).

Further discussion has been confined to electrophysiological tests since we used these in our project.

1.4 NEUROPHYSIOLOGICAL TESTING OF THE FUNCTIONAL INTEGRITY OF THE AUDITORY PATHWAYS

1.4.1 **Auditory evoked potentials**

Perception of sound can alter the electroencephalogram (EEG) of a listener (Davis, 1939). The EEG, altered as a result of the stimulus, generates what is termed as auditory evoked potentials. These are normally very small and rely on the process of signal averaging to amplify them. Scientific study through the 1960s and 1970s produced much literature focussing on auditory evoked potentials generated at the cortex including their neural generators and their physiological (acoustic and perceptual) and pathological variables. At the time, however, the variability of the cortical evoked potentials posed limitations for routine use in clinical populations such as infants and children at risk for neurologic and hearing impairment. The discovery of the auditory brain stem response further overshadowed the use of cortical evoked potentials in clinical audiology in the last decade of the twentieth century (Jewett & Williston, 1971). In the 1990s, interest in cortical evoked potentials was once again ignited with research indicating that cortical potentials could be employed for determining sound discrimination abilities (Kraus, Koch et al., 1999) and for identifying auditory perceptual processing disabilities related to learning disorders (Kraus, McGee et al., 1996; Cone-Wesson & Wunderlich, 2003)

Evoked potentials, generated by the nervous system in response to a specific stimulus are of small amplitude in comparison to the EEG and therefore extracted using an averaging technique that is dependent on the brain activity being time-locked to the presentation of the stimulus compared to the random background EEG. Averaging results in a reduction of the noise relative to the signal (signal / noise ratio) and is

proportional to √n, where n is the number of responses. The continuous EEG is epoched and analysed by a computer that sums waveforms within each of the individual epochs and then divides the summed waveform by the total number of EEG epochs. Evoked potentials are non-invasive, with millisecond by millisecond temporal resolution.

Human auditory evoked potentials (AEPs) are generally classified into early (0-8 ms), middle (8-90 ms) and late (90-500 ms) responses suggesting serial processing of auditory information (See Figure 10). However this sequential flow of information suggested by the AEP may be a simplistic representation of the underlying neuronal activity, and may not reflect sub-cortical pathways which may connect various auditory cortical areas together bypassing intermediate ones.

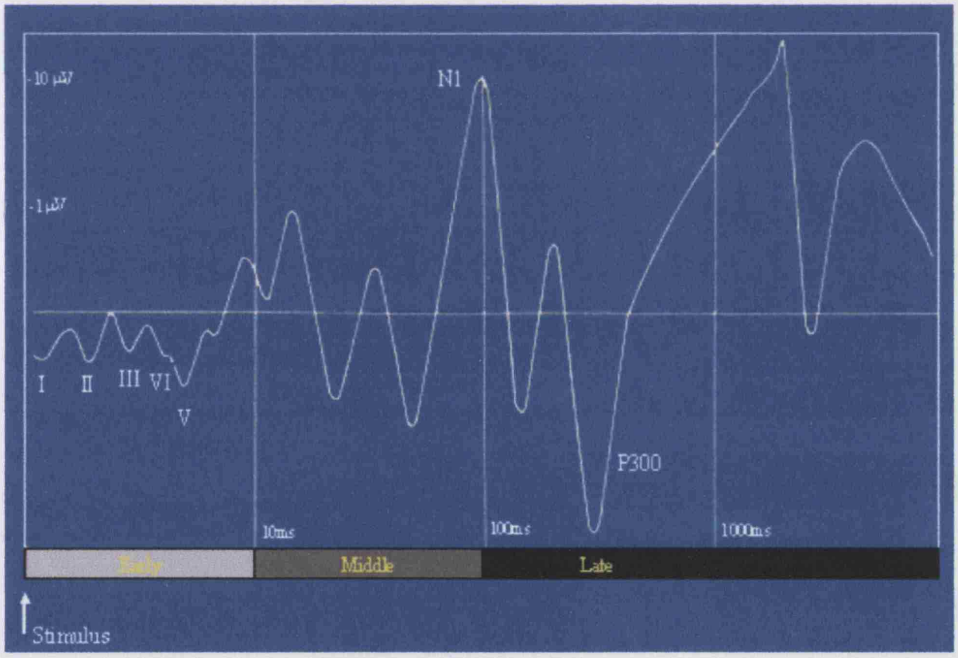

Figure 10: Schematic representation of potentials evoked following auditory stimulation. Both amplitude (μv) and latency (ms) are displayed using logarithmic scales. Potentials are grouped into three categories: early, middle and late. After (Cooper et al., 1980).

1.4.1.1 Acoustic vs electrical stimulation

Evoked potentials can be generated using both acoustic and electrical stimuli. Most of the research in the past has been conducted using acoustic stimuli. However the most common outcome of evoked response audiometry using acoustic stimulus in cochlear implanted candidates is total absence of all response components or occasionally some residual response activity. Identification of significant levels of response activity in one or both ears is important because this may influence the decision as to which ear to implant. Many young children who have acquired a profound hearing loss due to meningitis may show some recovery and therefore any response activity on evoked response audiometry should be examined very carefully to exclude as far as possible any improvement in hearing and in such cases the ear with least or no response should be implanted. An absence of all responses on evoked response audiometry although consistent with cochlear hearing loss, cannot exclude the possibility of retro cochlear pathology or neural damage, neither does it reflect the status of central auditory pathways.

There are two specific drawbacks in recording electrically evoked potentials: response contamination due to the spread of stimulus artefact to the recording electrodes and the determination of spread of stimulus to other than the target system as demonstrated by magnetic field evoked potentials (Kileny, 1991).

The different classes of electrically evoked potentials are directly related to their acoustical counterparts to the extent that similar terminology is often applied with a prefix 'E' to denote the electrical response.

The range of responses reported in literature includes:

- Electrically evoked compound action potential (EAP),
- Electrical auditory brain stem responses (EABR),
- Electrical middle latency response (EMLR),
- Electrical auditory cortical response (EACR)
- Event related potentials such as P-300 and mismatch negativity (MMN)

1.4.2 **Brain stem evoked response audiometry**

Early or brain stem auditory evoked potentials (BSAEPs) are elicited using rapidly presented brief stimuli such as clicks. Short duration stimuli are used to ensure no overlap of BSAEP components. BSAEPs are widely used to assess the integrity of the brainstem auditory system (Jiang & Tierney, 1995). The adult BSAEP consists of seven small positive deflections that usually occur with in the first 8 to 12 ms from stimulus onset (Legatt, Arezzo et al., 1988) but only components I, II, III, IV and V are used for clinical purposes (See Figure 11). The interpretation of BSAEPs can sometimes be problematic since certain waves can be absent or two waves may appear as one. Despite the lack of one to one correlation between the BSAEP components and anatomical structures, a clinically accepted classification of the BSAEP neuronal generators suggests:

- 'component I' corresponds to the distal portion of the V111th nerve,
- 'component III' mainly corresponds to the superior olivary complex and

- 'component V' corresponds to the termination of the inferior colliculus and to the lateral lemniscus (Moller, 1994).

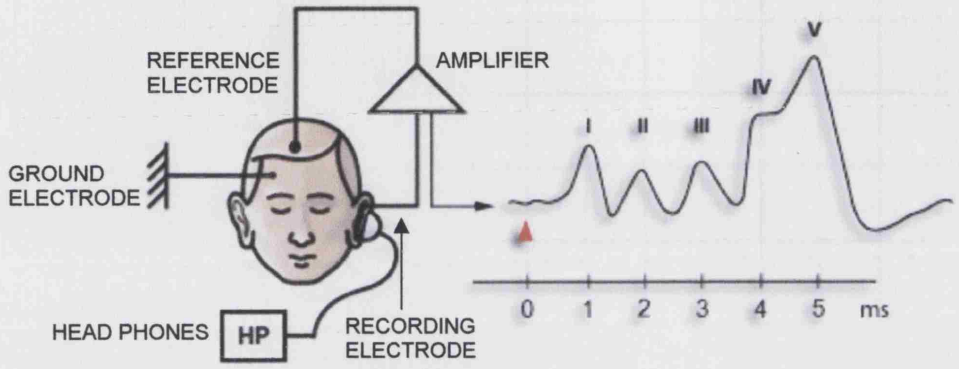

Figure 11: Diagram to illustrate recording and response of brainstem auditory evoked potentials (BSAEPs)

(With kind permission from Promenade round the cochlea, www.cochlea.org, R Pujol et al., Univ. Montpellier; Author of drawing: S Blatrix)

In cochlear implant subjects, electrical auditory brainstem responses are measured using standard averaging techniques and equipment. The implant is directly stimulated, using stimulation software available from most cochlear implant manufacturers. An individual or pair of intracochlear electrodes are repeatedly stimulated using the software. A trigger pulse is used to control initiation of sampling by the evoked potential measurement system. The main problem with such recording is the large stimulus artefact, associated with the electrical current used to stimulate the nerve, but broad filtering and alternating the polarity of stimulation to record the EABR can circumvent this problem (Abbas & Brown, 2000). With high intensity

stimuli, it is possible to identify most of the waves except for wave 1, which is almost always obscured by the stimulus artefact.

The wave 5 component is generally used to identify response thresholds. An important clinical question is the extent to which electrophysiological measures of threshold can replace behavioural testing. This issue is complicated by the different pulse rates of stimuli used for behavioural and electrophysiological measures. At high pulse rates, such as those used to programme Nucleus CI24 implants, temporal integration of stimulus energy can strongly affect behavioural thresholds, which tend to decrease. However EAP and EABR thresholds are not affected in this way. They do not change with increasing rate of stimuli. As a result, the highest correlation between electrophysiological and behavioural measures can only be seen at low pulse rates where temporal integration is not a factor (Abbas & Brown, 2000).

Perioperative transtympanic EABR is used for ear selection and to establish the ability of successful electrical stimulation in many centres. This is especially important in patients with bilateral cochlear malformations, such as common cavity deformities, and narrow or absent internal auditory canals and in patients with labyrinthitis ossificans due to the higher incidence of unilateral absent EABR in these patient groups. This test is supplemented with EABR obtained immediately after the insertion of the electrode array and the seating of the implants receiver. In the postoperative period, EABR is used to properly adjust the implants parameters and it also serves to be an excellent check of the functioning of the implant system and auditory pathway (Kileny, Zwolan et al., 1997). The presence of an EABR waveform confirms that the auditory nerve fibres and brainstem are responding to the electrical stimulation.

1.4.3 **Middle latency auditory evoked potentials.**

The middle latency auditory evoked potentials are the earliest responses from the auditory cortex, and comprise of at least six potentials that can be recorded from the scalp with latencies between eight to 90 ms. These are named as Na, Pa, Nb, Pb and rarely Nc and Pc. The Na (15 ms) and the Pa (30 ms) both lasting about 25 ms are the most reliably recorded in adults. These potentials show a great deal of intra- and inter-subject variability and the probability of recording them below the age of five is very low (Kraus, Smith et al., 1985a; Kraus, Smith et al., 1985b). The other main disadvantage of EMLR is that it is dependent on the psychological state of the patient and has a prolonged maturational period, further restricting its use in young children, particularly during sedation and general anaesthesia (Kileny & Kemink, 1987). However their role in adults in diagnosing auditory processing disorders is established (Musiek, Geurkink et al., 1984).

In cochlear-implanted patients MLRs are evoked using electrical stimuli with two main advantages:

1. Unlike the ABR in which wave 1 gets contaminated by the spread of electrical artefact, wave Pa of MLR is not contaminated due to its relatively remote time frame. The most robust component of the EMLR has a latency ranging from 25 to 35 msec in adults, which is slightly earlier than their acoustical counterparts

2. The second advantage is that it can be elicited using lower current level with longer duration pulses. With transtympanic stimulation it was found that in adults the electric MLR thresholds closely approximated behavioural promontory thresholds for the same stimuli (Kileny, 1991).

In patients with cochlear implants, intracochlear stimulation reveals good correspondence between EMLR, behavioural thresholds and dynamic ranges (Miyamoto, R. T., 1986). When compared to EABR, the threshold for EMLR has been found to be lower (Kileny & Kemink, 1987). Wave morphology and amplitude of EMLR, has also been found to be similar in pre-lingual and post-lingual deaf cochlear implant patients. This suggests that differences in speech perception between these two groups, is not caused by integrity differences in the neural generators of EMLR (Groenen, Snik et al., 1997).

1.4.4 **Long latency / Auditory event related potentials.**

Unlike the previously described evoked potentials, event-related potentials (ERPs), also termed 'long latency' potentials generally require an active state of consciousness on the part of the participant for their generation. There are two types of cortical auditory event related potentials – obligatory and cognitive. The obligatory ERPs are those whose presence, latency and amplitude are determined primarily by the acoustic parameters of the stimulus and the integrity of the primary auditory pathway. The obligatory auditory ERPs has four major components, P1, N1, P2 and N2 (Figure 12A). These are generated at the level of the primary auditory cortex and auditory association areas of the temporal lobe. The obligatory ERP components can be elicited by clicks, tone bursts, tone complexes and speech sounds. They can be recorded in awake and alert adults and are also present in new born, young infants and children although their latency, amplitude and scalp distribution undergo significant maturation during the first 6 years of life and proceeding through adolescence. Obligatory potentials are also labelled as 'exogenous' because their response

characteristics are determined by stimulus parameters that are 'exogenous' to the listener (Figure 12B).

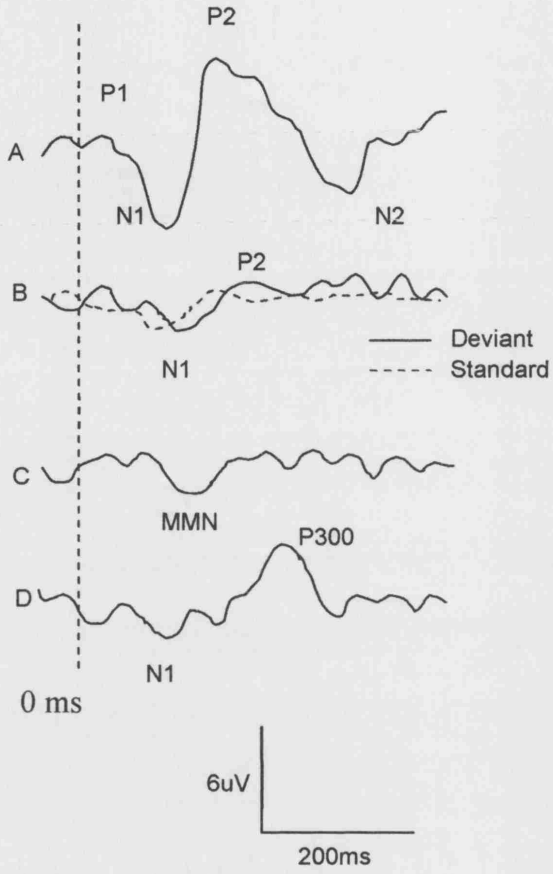

Figure 12: Event related potentials (A) ERPs in response to 400 Hz tone burst presented at ISI of 4600 ms, (B) attenuated response when presented at an inter stimulus interval of 750 $\pm$ 50 ms, (C) difference wave form (standard 440 Hz – deviant 400 Hz) resulting in MMN, (D) individual response to deviant showing P300. All responses recorded at Cz referred to the right mastoid with left mastoid as ground. After (Cone-Wesson & Wunderlich, 2003)

The endogenous or cognitive ERPs have characteristics which vary with the listener's attention to the stimulus and performance on cognitive tasks assigned while the responses are recorded. The stimulus used for these tests is presented in an 'odd ball paradigm.' The odd ball paradigm involves a standard or frequent stimulus presented

at 80 – 90 % probability and a deviant or target stimulus presented at 10 – 20 % probability (Figure 16). The main components of these endogenous or cognitive potentials are P 3 and MMN (Figure 12 C,D).

Long duration tone bursts can be used to evoke the obligatory ERPs. This is a distinct advantage over brain stem response methods for which transient stimuli must be used. The obligatory ERP threshold (5-19dB SL) is more closely related to perceptual threshold than ABR. The ERP has been proposed to be more indicative of how stimulus energy is integrated over time. Obligatory ERPs are currently used to estimate thresholds in awake alert adults who may be malingering (Hyde, 1997; Rickards, deVidi et al., 1996). In the case of infants and children, although the components can be recorded, the subjects need to be kept awake to obtain the recording, a practical difficulty which has not permitted it to be used in this age group. Also, since the ERP undergoes significant maturation in the first six years of life, age appropriate templates are needed to interpret the responses reliably.

1.4.4.1 Long latency N1 potential

ERPs recorded from the scalp are composed of overlapping and functionally distinct components having multiple generators. Wolpaw and coworkers in 1975 (Wolpaw & Penry, 1975) first suggested that multiple generators contribute to the scalp recorded auditory evoked N1. They recorded auditory ERPs from vertex and temporal locations, isolating a biphasic waveform recorded at temporal sites, which they termed the 'T-complex' (Tc). The Tc consists of a positive peak at 105 ms (Ta) and a negative peak at 155 ms (Tb). They suggested that the Tc was generated in the secondary auditory cortex on the lateral aspect of the temporal lobe, and that the NI/P2 recorded at the vertex was generated in widespread areas of the cortex,

particularly in the frontal regions. Apart from the Tc, it has been suggested that two more components contribute to the auditory evoked N1 (Naatanen & Picton, 1987). These consist of the auditory cortex (Ac) N1 (Vaughan & Ritter, 1970; Knight, Scabini et al., 1989), and a non-specific component (NSC) both with frontocentral topography. The source of the frontocentral NSC is not known, but is suggested to be in the frontal motor and pre-motor cortex (Naatanen & Picton, 1987) under the influence of the reticular formation and the ventral lateral nucleus of the thalamus.

1.4.4.2 Modulation of the long latency N 1 potential

The NI potential is evoked by an abrupt change in the level of the energy arriving at the sensory receptors (Barlow & Mollon, 1982). The amplitude and latency of the N1 potential can be modulated according to the stimulus characteristics and recording paradigm. The N1 increases in amplitude with increases in stimulus duration, up to 50 ms (Kodera, Hink et al., 1979). With an increase in stimulus intensity (James, Gordon et al., 1990) the N1 increases in amplitude and reduces in latency (Blenner & Yingling, 1993). Once high intensities have been reached the increase in amplitude levels off and even reduce in some cases (Picton, Goodman et al., 1970). The amplitude of the N1 is suggested to increase up to an ISI of 16 seconds (Hari, Kaila et al., 1982), while with less intense stimuli it reaches maximum amplitude at shorter ISIs. These data suggest that the recovery period of the N1 for intense stimuli is longer than for less intense stimuli.

The amplitude of an N1 evoked at the start of a train of stimuli is much larger than those evoked by subsequent stimuli as long as a silent period precedes the first stimulus. The large amplitude of the N1 to the first stimulus is suggested to be the result of activation of both the Ac N1 and the NSC, the latter not being evoked by

subsequent stimuli (Fruhstorfer, Soveri et al., 1970). Auditory ERP components are dramatically affected by sleep (Barnet, 1975), the major change being a decrease in amplitude of the N1 component and the emergence of the vertex sharp wave that is seen in the scalp EEG during sleep recordings.

1.4.4.3 Maturation of long latency N1 potential.

The central auditory pathways of the human brain undergo anatomical and physiological changes through early childhood. These changes are reflected in the latency, amplitude and morphology of auditory ERPs (Kraus, McGee et al., 1993). Although there is little work on the maturation of the auditory ERPs, the general consensus is that there are considerable age related changes of the major N1 components (Fuchigami, Okubo et al., 1993; Martin, Barajas et al., 1988).

In children as young as 6 years old, an N1 like component emerges at around 130 ms after stimulation (Bruneau, Roux et al., 1997) and can be more readily evoked if the ISI is prolonged (Martin, Barajas et al., 1988; Paetau, Ahonen et al., 1995). It has been suggested that this N1 recorded in children is not analogous to that recorded in adults (Csepe, 1995; Molnar, Skinner et al., 1995). In a MEG study it has been shown that the source of the NI in six to nine-year-olds has a different source localisation to that of adults (Reite, Adams et al., 1994). An adult-like N1/P2 complex is rarely obtained in children before the age of nine years (Ceponiene, Cheour et al., 1998).

The N1 in school age children (14-16 years) has a similar amplitude and latency to that of adults (Tonnquist-Uhlen, Borg et al., 1995) but quite different to that of infants (Kurtzberg, Vaughan et al., 1995). The N1 in children below the age of eight years has a topography maximal over the temporal electrodes while children above ten years have a shorter latency N1 with topography closer to the vertex (De Crevoisier,

Peronnet et al., 1975). This temporal dominance of the NI has also been reported recently when auditory ERPs were recorded in 4-8 year olds to pure tones (Bruneau, N., Roux, S. et al., 1997). The N1 evoked by pure tone shifts towards the right hemisphere with increasing age (Tonnquist-Uhlen, Borg et al., 1995). This shift in topography to the right hemisphere may reflect specialisation of the right hemisphere in the processing of non-speech stimuli.

1.4.4.4 P1 and N2 components; maturation with age

The ERPs of normal young children are dominated by a large positivity (P1) with a peak latency slightly earlier than that of the adult N1. This large positivity is followed by a negative trough at about 180ms which corresponds to the adult N2 although with a slightly shorter latency. It is not known however if these components are analogous to the adult P50-N1-P200 in terms of polarity or latency (Korpilahti & Lang, 1994). The N1 peak is not consistently present until the age of 9-10 years. By 12 -13 years, the ERP wave forms assume an adult like morphology with the N1 becoming increasingly negative with P1 decreasing in amplitude indicating that most of the reduction in P1 latency and amplitude could reflect phase cancellation of a mature P1 peak by amplitude increases in the maturing N1 peak (Ponton, Eggermont et al., 2000a) (See Figure 13).

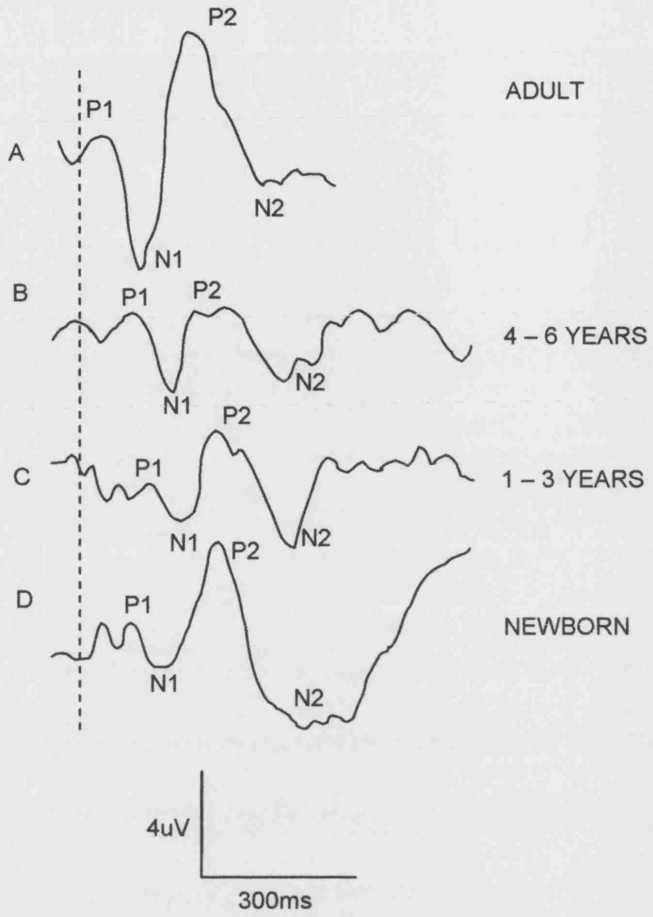

Figure 13 A: Event related potentials to the speech token 'bad' from different age groups. Responses were recorded from Cz referred to the right mastoid. After (Cone-Wesson & Wunderlich, 2003b)

P1 latency has been assessed as a function of age in normal hearing children and adults, ranging from 0.1 to 20 years (Figure 13 B) (Sharma, Dorman et al., 2002). Visual inspection of this data reveals that latencies decrease rapidly in the first decade of life and then decrease more gradually in the second decade of life. The best fit curve for the data was a growth function based on the natural log of age. These results have been consistent with other work reported by Sharma and co-workers (Sharma, Kraus et al., 1997) and Ponton and co-workers (Ponton, Eggermont et al., in 2000.)

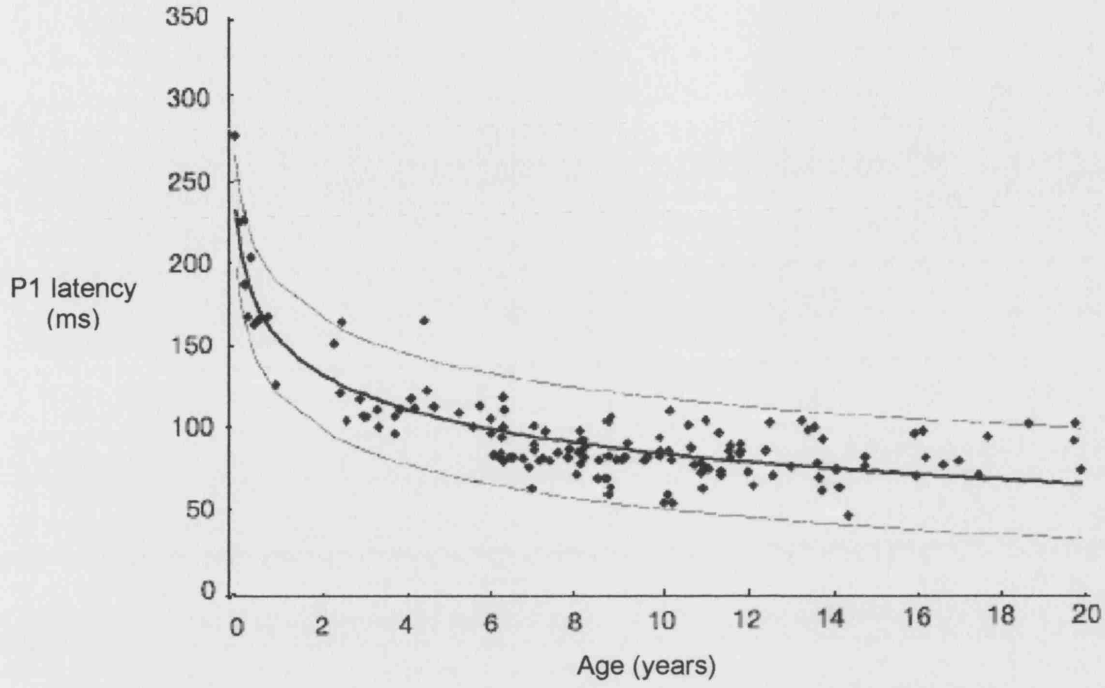

Figure 13 B: P1 latencies as a function of age for normal-hearing children. The best line of fit (bold) and 95% confidence intervals (grey) are superimposed on the raw data. (From Sharma, Dorman et al., 2002)

Age related differences in the effects of the rate of stimulus on the ERPs suggests different pathways of origin for the P1 and the N1 peaks. At stimulus presentation rate faster than 1/s, P1 is present over both hemispheres. N1 on the other hand, at stimulus rates of less than 1/s, is present only over the contralateral hemisphere, at least up to the age of 9 years. This suggests that a subcortical system projects bilaterally to the thalamic or cortical generators of the P1 peak and that a crossed subcortical pathway projects exclusively to the contralateral areas generating the N1. Work done by several researchers in this area suggests that P1 probably reflects activation of areas

bordering the secondary auditory cortex (Liegeois-Chauvel & Musolino, 1994). In contrast, the N1 peak reflects activation of the contralateral primary auditory cortex. (Elberling, Bak et al., 1982a; Elberling, Bak et al., 1982b; Pantev, Hoke et al., 1988). Further, the N1 has been attributed to intra- and interhemispheric cortico cortical inputs to the superficial layers (Javitt, Steinschneider et al., 1994; Makela & Hari, 1992; Makela & McEvoy, 1996). The sensitivity of the N1 to fast stimulus rates in children aged less than 9 years may reflect the immature state of axonal projection to these superficial cortical layers. This is supported by the emergence of the ipsilateral N1 peak after the age of 9 years which corresponds to the age at which these axonal projections to the superficial cortical layers become adult like. Analysis of age related changes in the cross sectional area (MRI based) of corpus callosum also indicates that the myelination of interhemispheric fibres becomes adult like at about the age of 12 years (Hayakawa, Konishi et al., 1989)

There are many discrepancies in literature with regard to description of auditory ERPs in children. This may be the result of a number of factors such as high rate of intra and inter-subject variability in auditory ERPs recorded in children. In most studies small sample sizes within broad age ranges cannot reliably map out developmental changes, particularly if these changes are small and progressive over a number of years. In addition, the overall pattern of maturation of auditory ERPs depends on the scalp locations at which the responses are recorded (Ponton, Eggermont et al., 2000a)

Cochlear implant children have evoked potentials similar to younger normal hearing children until the age of 10 years. Beyond 10 years, normal hearing children demonstrate a classical N1/P2 complex, but cochlear implanted children continue to

show the P1 N2 components (Ponton, Eggermont et al., 2000b). The overall latency of P1 response is delayed in children with cochlear implants, but the rate of maturation for the P1 latency remains the same as in normal children (Ponton, Don et al., 1996a). As such, maturational delay in reaching adult P1 latency corresponds closely with the mean duration of auditory deprivation before implantation superimposed on the normal maturational time frame (Eggermont, Ponton et al., 1997; Ponton, Don et al., 1996b). On this basis, Eggermont and co-workers suggested a model of auditory development in the presence of deprivation followed by cochlear implantation. They suggested that stimulation is necessary for maturation of the auditory system. Deafness "freezes" the synapses in an immature state and cochlear implantation "thaws" the system out of its frozen state after which it resumes normal development (Eggermont, Ponton et al., 1997). In a very recent study by Sharma and co-workers, P1 latency of children who were fitted with a cochlear implant by 3.5 years, was compared with the P1 latencies of their age matched peers with normal hearing. No significant difference was found between the two groups. This suggests that early implantation occurs in a central auditory system that is minimally degenerate and allows normal maturation. It is possible that significant degeneration sets in only after two to three years (Sharma, Dorman et al., 2002b).

1.4.4.5 Potentials evoked during an odd ball paradigm

Using an odd-ball paradigm where deviant stimuli (deviant probability $p = 0.10 - 0.12$) are embedded in a series of standard stimuli it is possible to study AERP components associated with discrimination processes.

These infrequent stimuli embedded in the sequence can evoke a number of components not seen in the response to standard stimuli. These components mainly

consist of the P3a, P3b, N2b and MMN. Odd-ball recordings can be carried out during an active or passive situation. During an active recording the subject is instructed to pay attention to the stimuli and perform a task when a specific stimulus is presented. For example a subject may be asked to count or press a button when a deviant stimulus is presented in a sequence of standard stimuli. During a passive recording the subject is asked to ignore all the stimuli and in some cases attention is further drawn away from the auditory stimuli by the subject reading a book or watching a silent video.

1.4.4.5.1 *P 3*

The P3 ERP has been widely used to study attention and memory mechanisms. It was first reported in 1965 (Desmedt, Debecker et al., 1965; Sutton, Braren et al., 1965) and has been extensively studied in normal, neurological and psychiatric population groups. It has been proposed that the P3 has two components, the P3a and the P3b. P3b is recorded mainly over the parietal area when a subject voluntarily detects an infrequent and task relevant stimuli. The P3 is evoked not only in the auditory system but also in visual, somatosensory, and olfactory sensory systems. The modality-specific nature of the P3b has been extensively studied. Topographic EEG studies in normal subjects (Barrett, Neshige et al., 1987; Johnson, 1989b), patients with temporal lobectomy (Johnson, 1989a) patients with callosotomy, and magnetoencephalographic studies in normal subjects (Rogers, Baumann et al., 1991) have demonstrated that there are modality-specific contributions to the P3b. One theory proposes that the P3b represents closure of voluntary stimulus processing in the association cortex (Verleger, 1988; Schupp, Lutzenberger et al., 1994). Another important theory supported by psychophysiologic research is that the P3b indexes

updating of activity in corticolimbic circuits during attention and working memory (Ruchkin, Johnson et al., 1990).

Involuntary orientation to an unexpected and novel stimulus generates a P3a response that is recorded over widespread anterior and posterior scalp areas (Knight, Scabini et al., 1989; Yamaguchi & Knight, 1991). The P3a has a more frontocentral scalp distribution than the P3b and peaks 60-80 ms earlier in all sensory modalities. Intracranial recordings in the visual, auditory, and somatosensory modalities have shown that multiple neocortical and limbic regions are activated during tasks that generate scalp novelty-dependent P3a potentials (Baudena, Halgren et al., 1995).

Although, theories have been proposed on attention and memory formulations to account for the cognitive basis of the P3, no clear consensus has actually emerged (Verleger, 1988). The main disagreement results from the fact that P300 does not represent a unitary brain potential arising from a discrete brain region or cognitive process. Instead, scalp positivities recorded around 300 ms post-stimulus presentation measure activation of multiple neo-cortical and limbic generators. This finding is based on scalp topographic studies in normal subjects (Ruchkin, Johnson et al., 1990), intracranial recording in epileptic patients (Baudena, Halgren et al., 1995) and lesion studies in neurologic patients (Yamaguchi & Knight, 1991).

P3 has been shown to be readily obtainable from cochlear implant (CI) recipients. The mean latency of the P3 is significantly longer in CI recipients than normal hearing people probably due to overall slower auditory processing due to previous auditory deprivation. It could also be due to increased difficulty of the task for CI recipients. It would be interesting to know if this pattern is also seen in younger patients who are implanted at a very early age and those with short duration of hearing loss. One would

expect that these CI recipients would show shorter latencies if not normal due to minimal auditory deprivation. Previous studies have shown that the P300 component can be elicited in children as young as 3 months without an active task, i.e. with passive listening (Kileny, 1991). In a study by Kileny and co-workers in 1991, P300 were recorded using both passive and active task paradigms in four children aged 9 – 14 years. A prominent P3 component was evident in three cochlear implant recipients with both the amplitude and latency exceeding that of the normal hearing subject. In another case of a twelve-year-old pre-lingually deaf CI recipient, although the subject had excellent detection capabilities, he was unable to distinguish between the frequent and target stimuli and was considered a poor performer. There was no evidence of P3 component in his traces. However N1 and P2 components were seen confirming signal detections. These examples suggest that if the patient has the capability to discriminate between frequent and target stimuli, a P300 component will be generated even in a passive condition. In the absence of discrimination, N1 and P2 help establish the patients' signal detection capability (Kileny, 1991). In another study by the same author in 1997, the effects of type of stimuli and specific contrasts on MMN and P300 were studied in 14 cochlear-implanted children. They also looked at the relationship between P3 and MMN and speech recognition scores in these patients. Although the type of stimulus had an effect on the peak latencies and amplitudes of P2 and P3 components, these differences were not found to be statistically significant. However a strong statistically significant relationship was identified between P3 and MMN amplitudes and latencies and speech recognition test scores. Increase in amplitudes and decrease in latencies of MMN and P3 were associated with higher speech recognition scores. These results strongly suggest that cognitive evoked potentials like MMN and P3 have the potential to be established as clinically useful techniques for

evaluating central auditory processing skills of young children with cochlear implants in whom behavioural measurements may be difficult and unreliable (Kileny, Boerst et al., 1997).

1.4.4.5.2 *Mismatch Negativity (MMN)*

The mismatch negativity (MMN) is a task independent auditory ERP component elicited by infrequent deviant sounds even when the subjects' attention is directed to other auditory or visual stimuli (Naatanen, Gaillard et al., 1978; Naatanen, Jiang et al., 1993; Naatanen, Schroger et al., 1993; Naatanen, Paavilainen et al., 1993; Naatanen, Teder et al., 1992; Alho, Woods et al., 1994a). The MMN peaks at 100-300 ms after an occurrence of sound change. It overlaps with other auditory ERP components and is best seen as a difference wave obtained by subtracting the ERP to standard sounds from the ERP to deviant sounds (Figure 14). It is recorded with largest amplitudes over the fronto-central scalp areas. This is explained by bilateral generator sources in the auditory cortices, with their activity summating over the fronto-central regions of the scalp (Scherg, Vajsar et al., 1989). These results have been supported by source modelling for the MEG counterpart of MMN, the 'MMNm' (Levanen, Ahonen et al., 1996; Alho, Winkler et al., 1998). Interestingly, while the MMN and MMNm to changes in non-phonetic auditory stimuli are elicited with larger amplitudes in the right hemisphere (Levanen, Ahonen et al., 1996; Tervaniemi, Kujala et al., 1999), the MMN and MMNm to phonetic changes get stronger contributions from the left hemisphere (Naatanen, Lehtokoski et al., 1997). Generation of the MMN in the auditory cortex has also been indicated by intracranial ERP recordings directly from the human cortex. However, scalp-current density (SCD) maps calculated from MMN scalp-potential maps suggest that in addition to the left and right auditory cortices,

MMN gets an additional contribution from the prefrontal cortex (Deouell, Bentin et al., 1998; Giard, Perrin et al., 1990). Moreover, attenuated MMNs have been recorded in patients with lesions of the dorso-lateral pre-frontal cortex (Alho, Woods et al., 1994b).

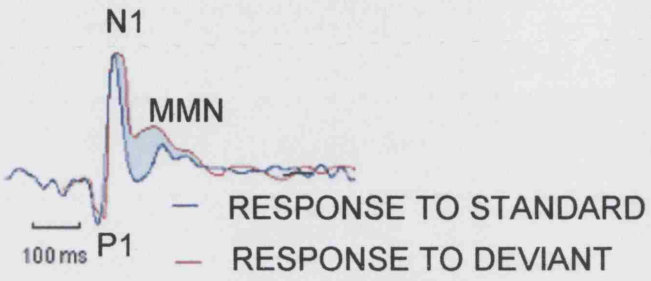

Figure 14: Event related potentials to standard and deviant sounds

It has been proposed that the MMN activity is generated by a mismatch between a deviant auditory input and auditory sensory memory representing the features of a repeating standard sound and that the frontal cortex contribution to the MMN is generated by prefrontal mechanisms initiating an involuntary switch of attention to changes in our auditory environment (Giard, Perrin et al., 1990). Studies have shown that MMN is not just a response generated by new non-refractory afferent elements activated by an occasional infrequent stimulus, but instead occurs in reaction to a change between standard and deviant stimuli (Cheour, Leppanen et al., 2000). This statement is based on the following evidence:

- First, the MMN is not elicited by the first stimulus in a series or when the inter stimulus interval (ISI) employed is very long, or when the deviant stimuli are presented alone (Cheour, Leppanen et al., 2000; Cowan, Winkler et al., 1993).

- Secondly, MMN can be elicited not only when stimulus intensity, duration or ISI are increased, but also when they are reduced. (Ford & Hillyard, 1981).

- Thirdly, MMN can also be elicited by omission of a stimulus (Yabe, Tervaniemi et al., 1997).

- Lastly, MMN latency and duration are relatively long for minor stimulus changes, which is atypical of basic afferent responses (Naatanen, Paavilainen et al., 1989a; Naatanen, Paavilainen et al., 1989b).

Based on this evidence it can be inferred that MMN is an outcome of a comparison process between a new deviant stimulus and a memory trace formed by the standard stimulus in the auditory system (Cheour, Leppanen et al., 2000). It therefore reflects the operation of auditory sensory memory, which in itself is a major pre-requisite for normal central auditory processing in the cerebral cortex. MMN is suggested to provide an objective measure of the automatic, pre-attentive processing involved in auditory discrimination and perception (Naatanen & Alho, 1995)and is thought to reflect high temporal resolution auditory discrimination processes in the time window of auditory sensory memory (Naatanen & Alho, 1997). Most of the early work on MMN has presented tones that differ in frequency, although more recently, tones that differ in duration (Joutsiniemi, Ilvonen et al., 1998), tone pairs (Csepe, Pantev et al., 1997) and speech sounds in an attempt to test for higher order phonemic processing (Kraus, McGee et al., 1995a)have been used.

MMN has been used in several studies to investigate neurophysiological plasticity following learning (Cheour, Leppanen et al., 2000). These studies have concluded that experience in a certain language environment can change MMN amplitude, latency,

or duration. Importantly, the results of behavioural studies can be related to the results of MMN studies. Krause and co-workers in 1995, demonstrated increase in duration, amplitude and area of MMN in adult subjects after one week of training to discriminate between two similar sounding variants of the phoneme /da/ and /ga/ (Kraus, McGee et al., 1995b). These effects of training were maintained one month after the last training session. Winkler and co-workers in 1999 showed that changes in MMN amplitude reflected neuronal plasticity in foreign language learning (Winkler, Lehtokoski et al., 1999). They studied Finnish speaking Hungarians, non-Finnish speaking Hungarians and Finnish subjects. The standard stimulus /e/ was a prototype in both languages whereas the deviant stimulus /ae/ was a prototype in Finnish but not in Hungarians subjects and /y/ which is a prototype in both languages. Their results also showed that /y/ elicited MMN of equal amplitude in all groups. However /ae/ elicited MMN only in Finnish and Finnish speaking Hungarians but not in the non-Finnish speaking Hungarians. Thus the results demonstrate that learning a foreign language is associated with neural sensory changes which are reflected by MMN.

1.4.4.5.2.1 *Modulation of MMN*

The MMN can be evoked to any change in the deviant stimulus characteristics from the standard such as frequency, interstimulus interval (ISI), intensity, pitch, rise time, duration or phonetic structure (Sams, Paavilainen et al., 1985). MMN amplitude increases and latency decreases with increased differences between the standard and deviant stimulus characteristics (Tiitinen, May et al., 1994). The MMN amplitude is affected by the probability occurrence of the deviant stimulus with the amplitude increasing with lower probabilities (Fitzgerald & Picton, 1983). MEG and EEG studies have shown that the sources for the different types of MMN have spatially

different loci (Sams, Kaukoranta et al., 1991; Liasis, Towell et al., 1999; Liasis, Towell et al., 2000; Liasis, Towell et al., 2001).

An MMN is not evoked when the neural representation of the standard stimulus no longer exists. This decay of the neural trace is reflected by the gradual decrease in amplitude of the MMN with increases in ISI resulting in no MMN being evoked with ISIs of 10 to 15 seconds (the duration of echoic memory as estimated by behavioural methods) (Sams, Hari et al., 1993). Although early research indicated that the MMN was independent of attention or task demands, recent studies have indicated that it can be modulated by attention. When attention is strongly focused on the input of one ear, the MMN to intensity deviance in the unattended ear may be reduced (Woldorff, Hackley et al., 1991). A number of studies have tried to record MMN during sleep, in cats (Csepe, Karmos et al., 1987) and in humans (Loewy, Campbell et al., 2000) but were only able to record MMN in REM sleep.

1.4.4.5.2.2 *Maturation of MMN*

Most MMN studies have been carried out in adults, but MMNs can also be recorded in response to changes in both non-phonetic and phonetic sounds in children.

1.4.4.5.2.2.1 *Babies*:

The earliest recording of a MMN has been in new-borns (Leppanen, Eklund et al., 1997). In full term new-borns, MMN was found to be similar in latency but smaller in amplitude to that of three-month-old infants (Cheour, Alho et al., 1998) and adults. In infants, MMN can be quite variable. It is sometimes even seen as a positive rather than negative displacement in response to the deviant sound (Morr, Shafer et al.,

2002; Dehaene-Lambertz, 2000). Generally it is present in infants as a broad negative displacement peaking at 100 – 250 ms.

MMN amplitudes exhibit change with age. In the majority of studies the MMN amplitude in school age children is larger than that found in adults (Csepe, 1995). Auditory ERPs are modulated by sleep and therefore sleep cannot be excluded as the reason for smaller amplitude MMNs in new-borns compared to that of three month olds. There are conflicting findings with respect to MMN latency. Shafer and co-workers (Shafer, Morr et al., 2000) observed some decrease in MMN latency in adults in comparison to 4 to 10 year olds who had longer latencies but others report adult like latencies from late childhood through adolescence (Kraus, Koch et al., 1999; Ponton, Eggermont et al., 2000a).

1.4.4.5.2.2.2 Children:

MMN can be evoked to speech and non-speech stimuli (pure sine waves) in school age children, although the scalp distribution depends on the type of stimulus. Pure sine waves and vowels have a fronto-central maximum slightly larger over the right hemisphere, while stop consonants evoked a larger response over the left hemisphere (Paavilainen, Alho et al., 1991; Csepe, Pantev et al., 1995). At school age it has also been shown that MMN can be evoked to just perceptible changes in speech stimuli, suggesting that MMN to just perceivable changes may be considered as a tool to investigate even subtle impairments of auditory perception in school age children (Kraus, McGee et al., 1993b). The most prominent difference between the MMN evoked by adults and children is that the area of MMN (peak to offset) in children is larger. The peak amplitude has been shown to be larger or the same as that evoked in

adults. Nevertheless most studies indicate that the latency and scalp distribution of the MMN in children does not differ significantly from those in adults.

1.4.4.5.2.2.3 Adults:

MMN recorded over the hemisphere contralateral to the stimulated ear appears to be adult like even in very young children. On the other hand MMN recorded over the hemisphere ipsilateral to the stimulated ear shows clear age related changes. In this hemisphere, up to the age of 7 years, no MMN is apparent in the ipsilateral hemisphere. After the age of 8 years, the MMN begins to emerge in this hemisphere gradually increasing in amplitude. As a result the ratio of magnitude of ipsilateral / contralateral shows an age related increase from approximately 0.2 in the 5-6 year olds to 0.6 in the 18-20 year olds. It has been proposed that the later emergence and amplitude growth of MMN over the ipsilateral hemisphere may reflect the late maturation of cortical mechanisms and interhemispheric connections in superficial cortical layers where the MMN is presumed to be generated (Ponton, Moore et al., 1999; Ponton, Eggermont et al., 2000a).

Overall, most MMN studies involving children indicate that MMN is developmentally quite stable in terms of latency and amplitude as compared to many other late component ERPs (Cheour, Leppanen et al., 2000). There are no big differences in MMN latency between adults and school age children (Kraus, McGee et al., 1993; Kraus, McGee et al., 1993b) although in infants the MMN latency tends to be somewhat longer (Kurtzberg, Vaughan et al., 1995; Cheour-Luhtanen, Alho et al., 1996).

Detailed account of MMN studies in cochlear implant patients has been included in section 6.4.

1.4.4.5.3 *Auditory event related potentials in clinical research*

Auditory event related potentials provide an ideal method for investigating neuronal processing of sound and speech, as they can be measured millisecond by millisecond. As such, they should provide powerful tools to study higher cortical functions such as cognitive processing and language. However, inspite of two decades of intensive experiments with MMN in many clinical fields, so far it has only found limited use as a diagnostic or prognostic measure in clinical practice. This is partly due to great inter-subject variability when assessed at an individual level compared to group average analysis (Cheour, Leppanen et al., 2000). McGee and co-workers investigated several different methods for determining response validity in individual subjects. They concluded that simple visual recognition of waveforms was insufficient to adequately judge MMN validity. This was due to an unacceptably high false positive rate shown in their study. They also concluded that point to point t tests although valuable in group data analysis, was not useful in analyzing individual responses. Their study concluded that combining area and latency criterion seemed to be the most sensitive method in individual MMN identification (McGee T., Kraus et al., 1997).

There is little question that MMN provides very useful information regarding processing of auditory stimuli at the level of cerebral cortex. It can be elicited without task vigilance, and therefore remains a strong candidate for objectively assessing auditory discrimination in young children or patients whose behavioural responses are compromised, such as young cochlear implant candidates (Ponton & Don, 1995)

1.4.4.6 Late Discriminative Negativity (LDN)

Apart from MMN, there is a second negativity that is related to changes in auditory stimuli, which can be elicited by passive oddball experiments using deviant stimuli. This negativity was first reported in children by Korpilahti et al in 1995 who called it the late MMN (Korpilahti, Lang et al., 1995). This negativity followed the MMN and peaked at about 400-450 ms in response to changes in speech stimuli and tones in 5 to 10 year old children and in young adults. In children the late MMN was significantly larger for deviant words than tones. In the case of adults, although the LDN response was elicited, it was of much smaller amplitude. The authors suggested that the LDN may reflect automatic processing of complex auditory stimuli. LDN in response to changes in complex auditory stimuli has been reported in adults by several authors (Alho, Woods et al., 1992; Trejo, Ryan-Jones et al., 1995). More recent work has demonstrated that the late negativity can also be obtained in response to changes in sinusoidal tones (Ceponiene, Cheour et al., 1998).

In contrast to MMN that matures early LDN has not proved to be a very stable response. Cheour and co-workers studied ERPs to deviant harmonic tones in 4 and 8 year old children and adults and found no difference between the age groups in the latency, amplitude or scalp distribution of MMN. LDN on the other hand was found to be significantly larger in children than in adults (Cheour, Korpilahti et al., 2001). They have suggested that the maturation of LDN resembles that of the negative component (Nc). The Nc, a frontally dominated negativity has been suggested to be a manifestation of attention to a recently presented stimulus, which is important enough to warrant more detailed processing (Symmes & Eisengart, 1971; Courchesne, 1978;

Courchesne, 1977). The Nc amplitude decreases with age so that in middle aged subjects, the Nc is not always detectable. The latency also decreases with development, being approximately 1000ms in newborns, 700ms in 6-month-old infants and adult levels of 400ms by the age of seven years. Most of these figures are based on experiments done in the visual modality. Investigations in the auditory modality are quite rare. Kurtzeberg and Vaughan in 1985 reported this negativity in infants in response to changes in the auditory stimuli (/da/ and /ta/). Although this response appears to be the auditory equivalent of the visual Nc, they have suggested that it is probably not analogous to the visual Nc because the stimuli used in the their experiment were not very new, surprising or important (Kurtzberg & Vaughan, 1985).

Some studies suggest that LDN has greater amplitude when elicited by speech stimuli than when it is elicited by tones (Cheour, Korpilahti et al., 2001; Korpilahti, Lang et al., 1995; Korpilahti, Salmela et al., 1997). Korpilahti and coworkers recorded ERPs in 5-10 year old Finnish children using the word /tu:li/ (wind) as standard and the word /tuli/ (fire) as a deviant. The two words are different in the duration of /u/ and in the formant structure of the two words. The deviant word elicited two negativities, one peaking at 250 ms (typical MMN) and the other peaking at 400-450 ms (Late MMN). They have reported that this late MMN reflects an automatic mismatch process at a complex auditory / linguistic level (Korpilahti, Lang et al., 1995).

Due to the relatively recent discovery of LDN, few clinical studies have been carried out looking at LDN in detail. In one of these studies, ERPs were recorded in a 5 year old language learning impaired child before and after an 8 month period of auditory discrimination training. The stimuli used were complex tones, naturally spoken words, and pseudo words. Auditory discrimination training led to a decrease in LDN

latency. This was suggested to reflect higher mental speed of auditory processing as a result of the training (Cheour, Korpilahti et al., 2001). Current lack of normative data for LDN makes it difficult to interpret its significance. More LDN data is needed especially from infants and children to establish the limits of normal variation and make age comparisons more reliable.

2 AIM OF THE STUDY

The aim of this study was to evaluate whether there was a correlation between auditory event related potentials to speech stimuli and measures of behavioural outcome in young cochlear implant patients.

3 MATERIALS AND METHODS

3.1 ETHICAL CONSIDERATION

The research received ethical approval from the Great Ormond Street Hospital for Children NHS Trust / Institute of Child Health Research Ethics Committee (Research and Development Reference Number 02NR36). All the subjects and their parents / guardians were given information sheets describing the study. The study and the procedure involved in carrying out the recording were also explained on a one-to-one basis prior to recording. All the patients and parents / guardians signed consent forms prior to participation in the study. Results of the study have been communicated to them.

3.2 INSTRUMENTATION

The recording equipment consisted of two synchronised systems, the EEG data acquisition / analysis system and an auditory stimulator. SCAN 4.2 software (Neurosoft, Inc. USA.) was used to acquire and analyse the data, while 40 channel NUAMPS amplifiers (Neurosoft, Inc.) were employed to amplify and digitise the cortical electrical signals. The auditory stimulator consisted of a computer running STIM VERSION 3 (Neurosoft Inc) to deliver auditory stimuli presented using sound field speakers.

3.3 METHODS

3.3.1 **Participants**

All patients on the Great Ormond Street Cochlear Implant Programme who were more than 7 years old at the time of carrying out the project and had received full insertion of a Nucleus multi-channel cochlear implants (Nucleus 22 / Nucleus 24M / Nucleus 24 Contour ; >20 electrodes) were approached for participation in the research project. 40 patients were finally recruited for the study. ERP recordings in 5 of these patients could not be included in the study due to contamination of the recording by artefacts generated by the speech processor and cochlear implant package. (See Section 4 for details)

The remaining 35 patients were included in the study. The patients age ranged from 7 to 17 years (mean age 12 years). Prior to surgery all patients had bilateral severe to profound sensorineural hearing loss (>70dB hearing threshold level). After surgery all subjects revealed pure tone thresholds to warbled tone stimuli in the 30 to 40 dB range. All 22 electrodes were active in all patients except one who had 20 active electrodes. All the patients used Nucleus BTE (behind the ear) speech processor with SPEAK speech coding strategy. Although some of these patients had used body worn speech processors at an earlier stage after implantation, they had used the same SPEAK speech coding strategy with it. 27 subjects were implanted on the right side and 8 were implanted on the left side. Two subjects were post-lingually and 33 were pre-lingually deaf. Of the 33 pre-lingually deaf, the hearing loss was congenital in 26 and acquired in 7. Length of implant use ranged from 1 to 10 years. None of the patients recruited in the study had any serious additional disabilities at this time. All patients had undergone a variable period of trial of hearing aids prior to implantation.

1 patient was using a hearing aid in the other ear concurrently at the time of the project (No. 31, Table III). Additional subject information on behavioural outcomes, age of the patient, aetiology and progression of deafness, time of implantation etc is provided in Table III.

3.3.2 **Stimuli**

Computer generated speech stimuli /ba/ and /da/ were used to elicit the event related potentials. These syllables were selected from a synthesized voice place-of-articulation continuum varying in the starting frequencies of their second and third formant (Werker & Lalonde, 1988) (See Figure 15). Both stimuli were 275 ms in duration. The fundamental frequency was steady at 100Hz for the first 100 ms, and then gradually rose to 120 Hz during the remaining 175 ms. The first formant (F1) rose from 250-500 Hz in a 50 ms transition while the fourth and fifth formants were constant at 3500 and 4000 Hz, respectively. The steady state for the second and third formants (F2 and F3) was 1090 and 2240 Hz respectively. The standard stimulus /ba/ had F2 and F3 frequencies of 900 Hz and 2240 Hz while the deviant stimulus /da/ had F2 and F3 frequencies of 1600 and 2912 Hz varying over 50ms to 1090 and 2440 Hz respectively. These particular /ba/ and /da/ stimuli have been reported to be reliably identified as /ba/ and /da/ and discriminated from one another behaviourally and electrophysiologically by British native English speakers (Rivera-Gaxiola, Johnson et al., 2000). The stimuli were delivered by a computer (Neuroscan-STIM Version 3) using sound field stimulation with loudspeakers placed 1 meter to either side of the patient (75 dbA).

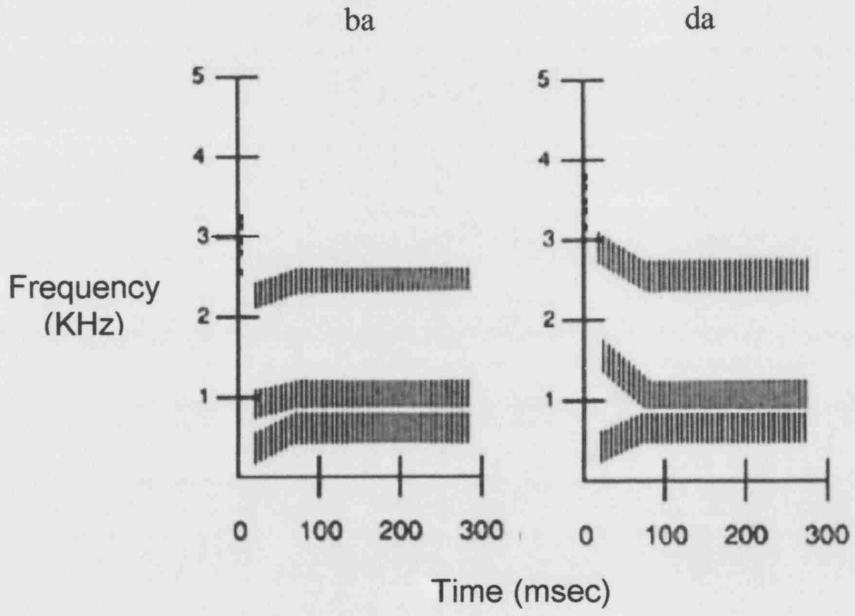

Figure 15: Spectral array of syllables /ba/ and /da/ used in our recordings. Note the major difference between the two stimuli is the first 50 ms of the second formant (Werker & Lalonde, 1988).

3.3.3 **Procedure**

The patients were allowed to make themselves comfortable and relaxed in the test seat. The entire test process was explained to them. They were instructed to watch the silent movie and not be disturbed by the background sound stimulus being played. They were instructed to keep their head as still as reasonably possible during the recording and not fall asleep. All patients undertook passive oddball auditory tasks involving consonant-vowel syllables. During all recordings, a pseudorandom sequence of stimuli was presented with a deviant probability equal to 0.12. This ensured that the responses being compared between patients were evoked by identical sequences and, more importantly, the sequence could be structured to ensure no two deviants were presented one after the other, which would contaminate the auditory ERPs by possibly evoking a MMN to the standard stimuli as a result of reinforcing a standard memory trace of the deviant stimulus. Figure 16 illustrates the pseudo-random sequence used in our study. Throughout the recording, the patients watched a silent movie of their own choice on a computer monitor placed one metre in front of them, in order to minimise head and eye movements. The entire recording was obtained during passive listening.

The inter-onset Inter Stimulus Interval (ISI) was set at 1000 msec. The stimuli were presented in 4 blocks of 500 stimuli containing 60 deviants /da/ and 440 standards /ba/ for each subject. As a control, 1 block of 200 presentations of /da/ was presented alone (/da/ alone condition), also at 1/second. The same sequence of test and control stimuli was presented to all the patients in exactly the same order. The researcher

carrying out the tests was blinded to the scores of behavioural outcome of the patients at the time of doing the tests and processing the recordings.

AAAAAAABAAAAAAAAABAAAAAABAAAAAAAAAAABAAAAAAAAAAAABA
AABAAAAAAAAAAAAAABAAABAAAAAAAAABAAAAAAAABAAAABAAAB
AAAAAAABAAAAAAAAABAAAAAABAAAAAAAAAABAAAAAAAAAAAAB
AAABAAAAAAAAAAAAABAAABAAAAAAAABAAAAAAAAABAAAAABA
AAABAAAAAAABAAAAAAAABAAAAAABAAAAAAAAAABAAAAAAAAA
AAABAAABAAAAAAAAAAAAAABAAABAAAAAAAABAAAAAAAABAAAA
BAAABAAAAAAABAAAAAAAABAAAAAABAAAAAAAAAABAAAAAAAA
AAAAAAABAAAAAAAAAAAAAABAAABAAAAAAAABAAAAAAAABAAA
AABAAAABAAAAAAABAAAAAAAABAAAAABAAAAAAAAAAABAAAAAA
AAAAAABAAABAAAAAAAAAAAAABAAABAAAAAAAABAAAAAAAABA
AAAAAAAABAAAAAAAABAA

Figure 16: Sequence of stimuli.

[The identical sequence was used in all recordings. A= standard /ba/, B= deviant /da/.]

3.3.4 **Data acquisition**

Twenty one silver-silver chloride electrodes were employed to record the electroencephalographic activity [Fz, F3, F4, Cz, C3, C4, T3, T4, Pz, P3, P4, Oz, O1, O2, T5, T6] employing a modified 10:20 montage (Le, J., Lu, M. et al., 1998). The reference electrode was placed at the mastoid contra lateral to the side of cochlear implant while the ground electrode was placed on the subjects' forehead. An electrode placed above the contralateral eye to the side of implant was used for artefact rejection of eye blinks online. Electrodes were attached to the scalp using Elefix cream (Nihon Kohden Ltd) after scalp preparation using Neuroprep. The impedance of the electrodes during the recordings was maintained below 5 KOhms. The cochlear implant and speech processor device were kept at the individual patients' standard comfortable settings. The continuous electroencephalogram (EEG) was

collected at a sampling rate of 1000 Hz, with a band pass of 0.1–100 Hz and stored on a PC for further processing.

3.3.5 **Data processing**

The continuous EEG data was digitally filtered off-line with a low pass of 30 Hz and a 12 dB/oct roll-off, and analysed as epochs of -100 to +900 ms post-stimulus presentation. The zero base line was defined as the average voltage of the pre-stimulus base line (-50 to 0 ms). Artefact rejection of epochs containing transients greater than $\pm$ 100 μV was carried out off-line.

Latencies and amplitudes of the following components were investigated: P1, N1, P2, N2, MMN and LDN from electrodes Fz, F3, F4, C3 and C4. Deviant, standard (excluding the post-deviant standards) and deviant alone ERPs were constructed. All ERPs were constructed from a minimum of 100 epochs. Peak latency and amplitude of P1 and N2 was measured from the 'standard' ERP (/ba/ standard). The MMN was analysed as a difference wave obtained by subtracting the 'deviant alone ERP' (/da/standard) from that of the 'deviant' ERP (/ba/standard, /da/ deviant).

The MMN was defined as a visually identified negativity in the subtraction waveform peaking between 100 and 350 ms post-stimulus presentation by two experienced scientists. For each difference waveform the onset, peak and offset latency was measured. MMN duration was calculated as offset minus onset latency.

The reproducibility of MMN was assessed by comparing averages constructed from equal numbers of random epochs and, odd and even averages extracted from the complete data sets. If the MMN identified in the subtraction waveform was not

reproducibly present in the sub-averages in any of the above-described averages, then it was not regarded as a true MMN.

The LDN was defined as a visually identified negativity in the subtraction wave form peaking after 500 ms post-stimulus presentation by the same two experienced scientists. For each difference waveform the onset, peak and offset latency was measured. LDN duration was calculated as offset minus onset latency. The reproducibility of LDN was assessed and confirmed in the same way as for MMN.

3.3.6 **Behavioural assessment**

Overall behavioural measures of these patients were obtained from two scores: Category of Auditory performance score (CAP) and Speech Intelligibility Rating scores (SIR) based on observations by their respective teachers of the deaf and speech and language therapists at the time of their last evaluation. (Tables I and II).

	CAP SCORE
0	No awareness of environmental sounds
1	Awareness of environmental sounds
2	Response to speech sounds (e.g. go)
3	Identification of environmental sounds
4	Discrimination of speech sounds
5	Understand common phrases, no lip reading
6	Understands conversation, no lip reading
7	Use of telephone – known speaker

Table I: Category of auditory performance (CAP) score

	SIR SCORE
1	Pre-recognizable words in spoken language
2	The primary mode of communication is manual. The speech or vocalization patterns which accompany the use of sign / gesture may give some additional information at the lip reading level.
3	Speech is unintelligible. All experienced listeners can follow a known topic via lip reading and context clues. It is not possible to follow an audio tape sample.
4	Connected speech is intelligible to a listener who concentrates and lip reads.
5	Connected speech is intelligible to a listener who has a little experience of a deaf person's speech.
6	Connected speech is intelligible to all listeners. Child is understood easily in everyday contexts

Table II : Speech intelligibility rating (SIR) score

The CAP score is a standard scale used to rate outcomes from paediatric cochlear implantation in everyday life. It is an eight point hierarchical scale of auditory performance, ranging from no awareness of environmental sounds (score 0) to use of the telephone with a known speaker (score 7) (Archbold, Lutman et al., 1995). It is different from more technical measures by being readily applied and easily understood by non–specialist professionals and parents. The CAP score has previously been assessed and shown to demonstrate high inter-user reliability based

on extremely high degree of agreement between users establishing it as a very useful and robust outcome measure in cochlear implanted children (Archbold, Lutman et al., 1998). The SIR score is an effective global outcome measure of speech production in real life situations and has been used reliably in cochlear implant patients (Dyar 1994; Parker & Irlam, 1995). It ranges from 1 (pre-recognizable words in spoken language) to 5 (connected speech intelligible to all listeners, child understood easily in everyday contexts) (Allen, Nikolopoulos et al., 1998), although in the present investigation score 2 was expanded into a further two categories resulting in a 6 category scale, as this has been the practise at Great Ormond Street Hospital for the last ten years. Studies investigating the reliability of the SIR scale have found a high rate of agreement between observers using this measure to assess the speech intelligibility of deaf children after cochlear implantation. It is therefore regarded as a very useful tool by parents and local professionals involved in the care of cochlear implant patients (Allen, 2001).

In this study patients with a CAP score of 7 or SIR score of 6 were categorized as 'star' performers. Those with a CAP score of ≤ 5 or SIR score ≤ 3 were categorized as 'poor' performers.

3.3.7 **Statistical analysis**

The amplitude and latency parameters of ERP components were compared with measures of behavioural outcome (CAP and SIR scores) using independent t tests and bi-variate correlations.

The relationship between occurrences of MMN / LDN and CAP / SIR score was assessed using Pearson's chi-square and Fishers exact probabilities.

The symmetry of the responses evoked by the subjects was investigated by comparison of component amplitudes, latencies and duration over the frontal (F3, F4) and central (C3, C4) sites using paired t-tests.

Maturational trend of ERP components were investigated by analysis of their latency, amplitude and duration in pre-lingually deaf children. The two post-lingual patients were excluded from this analysis because maturation of the ERP components in these two patients would be similar to that of a normal hearing patient of the same age and in this respect not fit in the same model describing maturational trends in pre-lingually deaf cochlear implant subjects. Latency and amplitude measures were plotted against age of the patients and 'duration of implant use (time in sound).' Any relationship was investigated for linear, logarithmic, quadratic, and exponential trends.

Normality assumptions for all the above tests were investigated and where appropriate non-parametric tests were carried out. (See Appendix 3)

4 **ARTEFACTS**

One of the major factors that limited the recording of sound field stimulation evoked potentials in CI children in our study was the time locked artefact that the implant package and speech processor generated in response to speech stimulus. This was observed in the first five patients recruited for the study.

A number of studies investigating MMN in cochlear implanted patients using electrical pulses, tonal and speech stimuli have been carried out (Firszt, Chambers et al., 2002; Kileny, Boerst et al., 1997; Kraus, Micco et al., 1993; Ponton & Don, 1995; Ponton, Eggermont et al., 2000a; Ponton & Eggermont, 2001). Ponton and co-workers

have described the presence of artefacts when using speech stimuli in recording MMN in cochlear implant patients. Depending on the proximity of the scalp electrode they have described a stimulus artefact to be typically 10-100 times larger than the auditory evoked potential. They have suggested that these artefacts are not seen when using tonal stimuli or electrical pulses since these short duration stimuli separate the large stimulus artefacts produced by the implant from the epoch containing the AEP peaks of interest. The other method of dealing with artefacts is the use of filters. A 21 Hz low pass filter has been shown to be quite effective in dealing with artefacts especially high frequency activity such as EMG and fast EEG beta rhythm without causing any distortion of the MMN wave forms (Lang, Eerola et al., 1995).

Many earlier researchers did not face the problem of artefacts, as their patients used body worn speech processors, as opposed to the more proximal 'behind-the-ear' speech processor, that affect the electroencephalogram to a lesser degree due to the distance from the recording electrodes. Behind-the-ear speech processors have come into use since 1996. Also use of montages with small number of recording electrodes away from the implant and speech processor such as the use of a single frontal electrode Fz may not obviously reveal the artefacts since they are better characterized in the electrodes closer to the implant package and speech processor.

Based on our observations in the first five patients included in our study, we derived a methodology for an effective way of dealing with the majority of these artefacts introduced by speech stimuli. As one would expect, these artefacts were located primarily in the channels surrounding the cochlear implant coil and post-aural speech processor, with amplitude of 100-2000μV (Figure 17). However these artefacts also spread to all the other recording sites even though this was not always apparent in the

online continuous recordings. The use of filters did not prove to be effective in dealing with these artefacts.

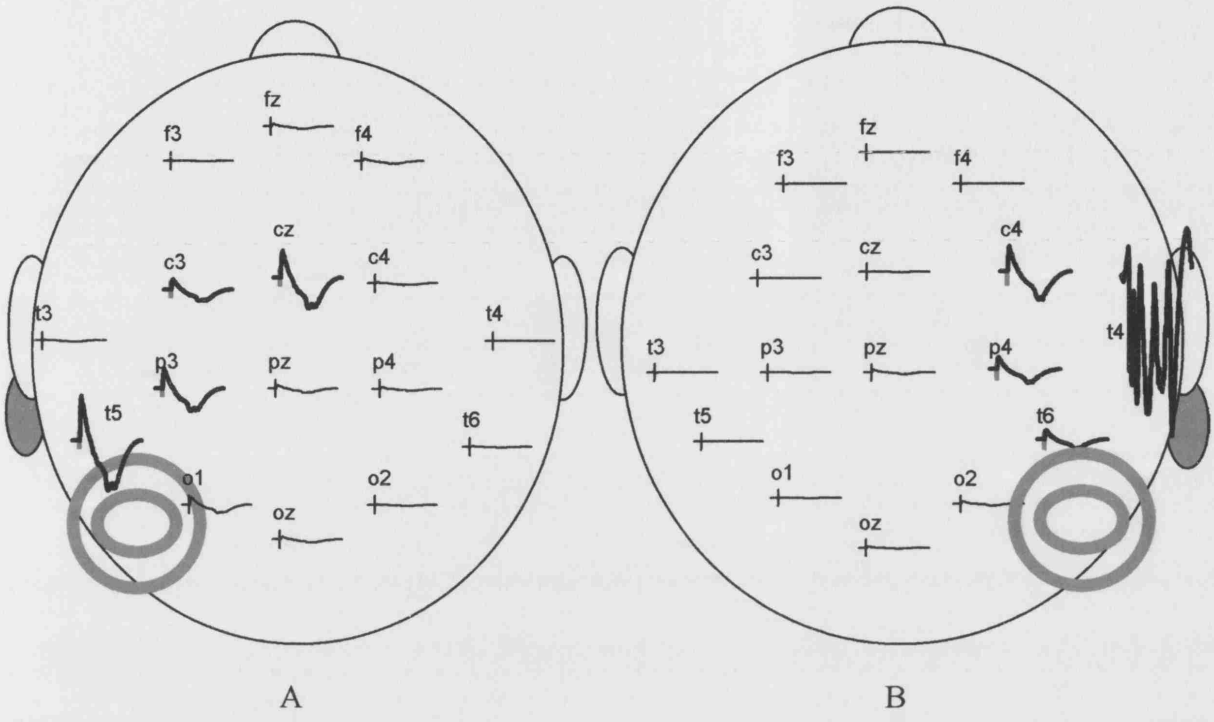

Figure 17: Distribution of artefacts (bold) in (A) left and (B) right cochlear implant patients

The majority of these artefacts were probably eddy current potentials that were picked up by the electrode leads in the vicinity of the speech processor and the implant. By reorienting the leads and bunching them away from the side of the implant, these eddy current potentials were reduced in amplitude, significantly improving the signal to noise ratio. Although bunching of electrodes is an established technique to improve the quality of evoked potential recordings, in the context of cochlear implant patients, it is important to realign the electrodes in a manner such that each individual scalp electrode is travelling to the opposite side from that of the implant as indicated in Figure 18. The beneficial effect of realignment can be verified by confirming the

disappearance of the artefact from the online continuous recordings before starting the actual recording (Figure 19).

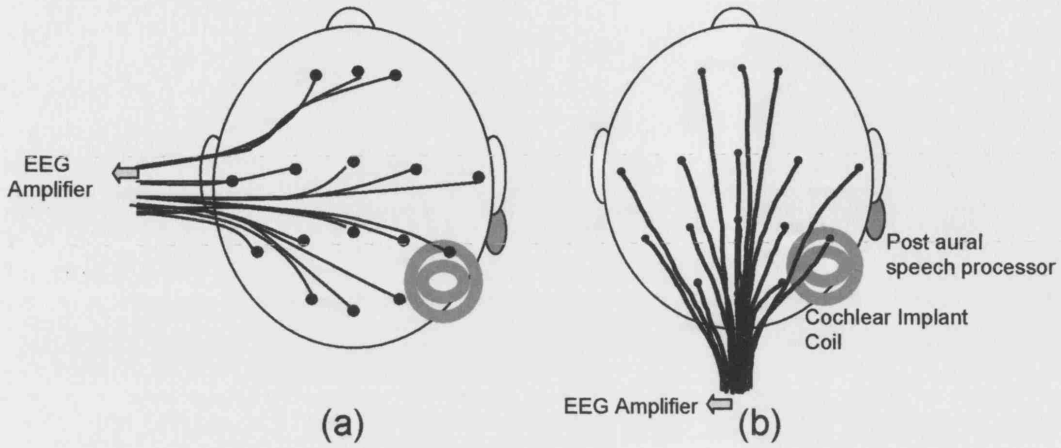

Figure 18: Repositioning of electrodes directed away from the implant (a)reduces artefacts significantly compared to conventional bunching of electrodes at the back(b)

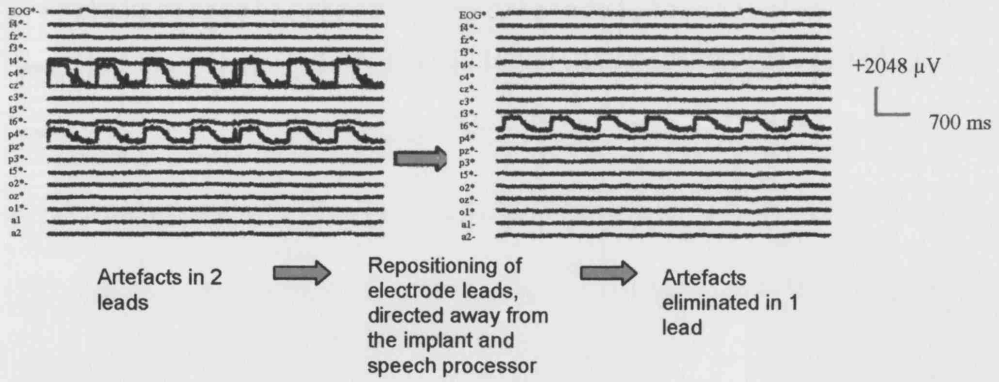

Figure 19: Continuous EEG recording demonstrating realignment of electrodes reduces artefacts.

We also attempted to tackle any residual artefact mathematically during offline analysis. We achieved this at first by creating an average of the artefact from one of the contaminated recording channels and then subtracting this from all the channels and all epochs proportionately, after first calculating their transmission coefficients. Although the above technique was useful in 3 out of our 5 patients with contaminated recording, we did not need to use any such processing in the remaining patients in our study since the steps involving realignment of electrodes proved adequate to acquire good quality recordings.

Using the above techniques we managed to improve the quality of our recording significantly. Although we were unsuccessful in recording ERPs to speech stimuli in the first five 5 patients, we were successful in recording ERPs in the remaining 35 cochlear implant patients in response to speech stimuli.

5 RESULTS

Details of subjects included in the study are listed below (Patients 1–20: Table IIIa; Patients 21–35: Table IIIb).

Patient No	Age of profound deafness (years)	Age at implantation (years)	Duration of implant use (years)	Age at test (years)	Side	Sex	Onset	Progression P/N	Aetiology	Last CAP Score	Last SIR Score
1	2.5	8	8.8	16.8	R	M	A	P	Rubella	7	5
2	15	15.3	1	16.4	L	F	A Po	N	meningitis	7	6
3	10.5	12.9	3.1	16	R	M	A Po	N	meningitis	7	6
4	B	4.8	10.1	15	L	M	C	N	unknown	7	3
5	9	11.3	6.4	17.7	R	M	A	P	meningitis	7	5
6	B	2.3	9.1	11.5	R	M	C	N	AR	7	6
7	B	3	8.1	11.1	R	F	C	N	unknown	7	6
8	3	6.7	10.1	16.9	L	F	A	P	CMV	6	4
9	B	4	7.3	11.3	L	M	C	N	unknown	6	3
10	1.5	4.4	9.3	13.8	L	M	A	N	meningitis	6	4
11	B	6.9	7	13.9	R	F	C	N	unknown	6	3
12	B	5.7	6.3	12	R	F	C	N	unknown	6	3
13	B	2.8	8.3	11.2	R	M	C	N	unknown	6	4
14	B	2.3	5.3	7.7	R	F	C	N	unknown	6	5
15	B	4.4	5.7	10.2	R	F	C	N	waardenburg	5	2
16	B	9.2	6.4	15.7	R	M	C	N	AR	5	3
17	B	4.8	6.3	11.1	R	F	C	N	unknown	5	3
18	B	4.4	10.3	14.7	L	F	A	N	birth hypoxia	5	4
19	B	5.4	6	11.5	R	M	C	N	AR	5	3
20	B	3.2	7.3	10.5	R	M	C	N	waardenburg	5	2

Table IIIa: Patient demographics; age of profound deafness, age at implantation, duration of implant use, age at test, side of implant, sex of patient, onset of deafness, progression of deafness, aetiology, CAP and SIR scores (obtained within 3 months of ERP recording). B: At Birth, A: Acquired pre-lingual, Po: Post-lingual, C: Congenital, P: Progressive, N: Non-progressive (based on clinical history), AR: Autosomal recessive, R: Right, L: Left, CMV: Cytomegalovirus infection

Patient No	Age of profound deafness	Age at implantation (years)	Duration of implant use (years)	Age at test (years)	Side	Sex	Onset	Progression P/N	Aetiology	Last CAP Score	Last SIR Score
21	B	5.9	8	14	L	M	C	N	AR	5	3
22	B	7	9.4	16.4	R	M	C	N	AR	5	3
23	9	12	1.6	13.7	R	M	C	P	AR	5	6
24	B	5.6	5.4	11	R	F	C	N	waardenburg	5	2
25	B	4.7	7.2	11.9	R	M	A	N	birth hypoxia	5	3
26	B	4.8	7	11.8	R	M	C	N	AR	5	4
27	B	6.3	4.2	10.5	R	F	C	N	ushers	4	2
28	B	3.1	5	8.2	R	M	C	N	ushers	4	3
29	B	4.2	3	7.3	R	F	C	N	unknown	4	3
30	2	4.6	5	9.7	L	M	A	N	meningitis	4	3
31	B	6.1	1	7.2	R	F	C	N	unknown	4	4
32	B	6.6	1.3	7.9	R	F	C	N	AR	4	4
33	10	13.2	1.1	14.3	R	F	C	P	AR (connexin 26)	4	4
34	B	6.7	3	9.8	R	F	C	N	unknown	4	1
35	B	2.2	5.4	7.6	R	M	C	N	AR	3	3

Table IIIb: Patient demographics; age of profound deafness, age at implantation, duration of implant use, age at test, side of implant, sex of patient, onset of deafness, progression of deafness, aetiology, CAP and SIR scores (obtained within 3 months of ERP recording). B: At Birth, A: Acquired pre-lingual, Po: Post-lingual, C: Congenital, P: Progressive, N: Non-progressive (based on clinical history), AR: Autosomal recessive, R: Right, L: Left, CMV: Cytomegalovirus infection

The 35 patients included in this study had varied aetiologies, onset and progression of deafness as detailed in the table above. Based on CAP scores, 7 patients were categorised as 'star' performers (CAP=7) and 21 patients were categorised as 'poor' performers (CAP $\leq$ 5). Based on SIR scores, 5 patients were categorised as 'star' performers (SIR= 6) and 19 patients were categorised as 'poor' performers (SIR $\leq$ 3).

5.1 OBLIGATORY COMPONENTS

Auditory ERPs in response to standard stimuli were identifiable in 30 out of 35 patients. Of these patients, 24 cases suffered from congenital deafness, 4 cases from acquired pre-lingual deafness, and 2 cases were post-lingually deaf. (Table IV)

	ERPs (P1 - N2)	
Aetiology	**Absent**	**Present**
Pre-lingual		
Infections (Rubella, CMV)	1	1
Congenital	2	24
Meningitis	1	2
Perinatal hypoxia	1	1
Post-lingual		
Meningitis	0	2

Table IV: Obligatory components (P1 – N2); occurrence based on aetiology

Grand averages of all patient data revealed responses consisting of a major positivity (labelled P1) followed by a negativity (labelled N2) (Figure 23A). The mean latency of P1 and N2 was 109.27 ± 24.78 msec and 241.03 ± 35.78 msec respectively. The mean amplitude of P1- N2 was 6.83 ± 3.54 μV. The N1 and P2 components were absent in all recordings in this study.

An assessment of the symmetry of responses over the frontal and central electrodes revealed no significant differences in the peak latency or amplitude of P1 and N2 components between the right and left electrode sites [C3 to C4 (Latency: P1, t=-0.42, P=0.68; N2, t=-1.6, P=0.10, Amplitude: P1-N2, t= -0.83, P=0.41] and F3 to F4 (P1, t=-1.8, P=0.08; N2, t=1.69, P=0.10, Amplitude: P1-N2, t= -0.61, P=0.54)].

Independent t tests comparing P1, N2 latency and P1-N2 amplitude in star performers (CAP 7 or SIR 6) and in poor performers (CAP </=5 or SIR </=3) categories did not reveal any statistically significant difference. Bi-variate correlation analysis assessing the relationship of obligatory components (latency and amplitude of P1 and N2) with behavioural score (CAP and SIR score) also did not reveal any significant relationship (Figure 20A–F). Latency and amplitude measures of these components across all behavioural groups are detailed in Table V.

	P1 Latency (ms)	N2 Latency (ms)	P1 N2 amplitude (μV)
	Mean ± SD		
All Patients	109.2 ± 24.7	241.0 ± 35.7	6.8 ± 3.5
CAP 7 n=7	103 ± 32.1	238.5 ± 35.8	5.9 ± 3.8
CAP 6 n=6	112.1 ± 21.7	241 ± 16.4	6.5 ± 2.9
CAP 5 n=10	105.7 ± 31.1	232.6 ± 41.3	7.6 ± 4.4
CAP </=4 n=7	115.7 ± 12.7	254 ± 41.3	6.6 ± 3.0
SIR 6 n=5	113.8 ± 39.8	241.8 ± 28.0	6.2 ± 3.7
SIR 5 n=3	99.3 ± 4.7	205.5 ± 16.2	3.9 ± 0.3
SIR 4 n=7	113.8 ± 14.9	253.4 ± 37.9	8.4 ± 3.1
SIR </=3 n=15	107.5 ± 26.1	241.4 ± 38.5	6.9 ± 3.8

Table V: Latency and amplitude of obligatory components in different behavioural groups based on CAP and SIR scores.

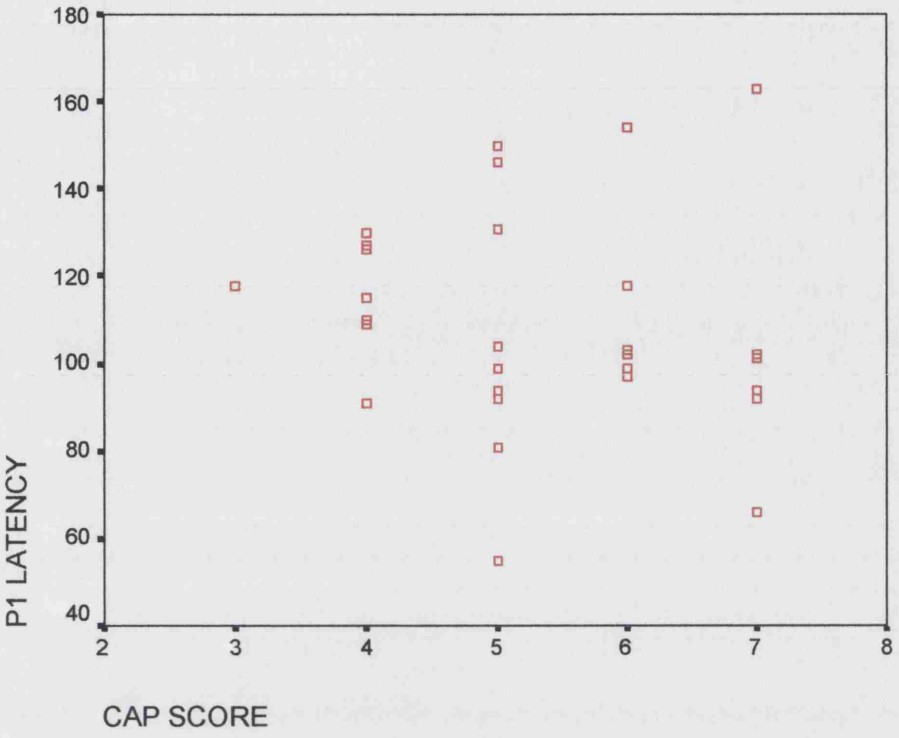

Figure 20 A: P1 latency (ms) vs Category of auditory performance (CAP) score

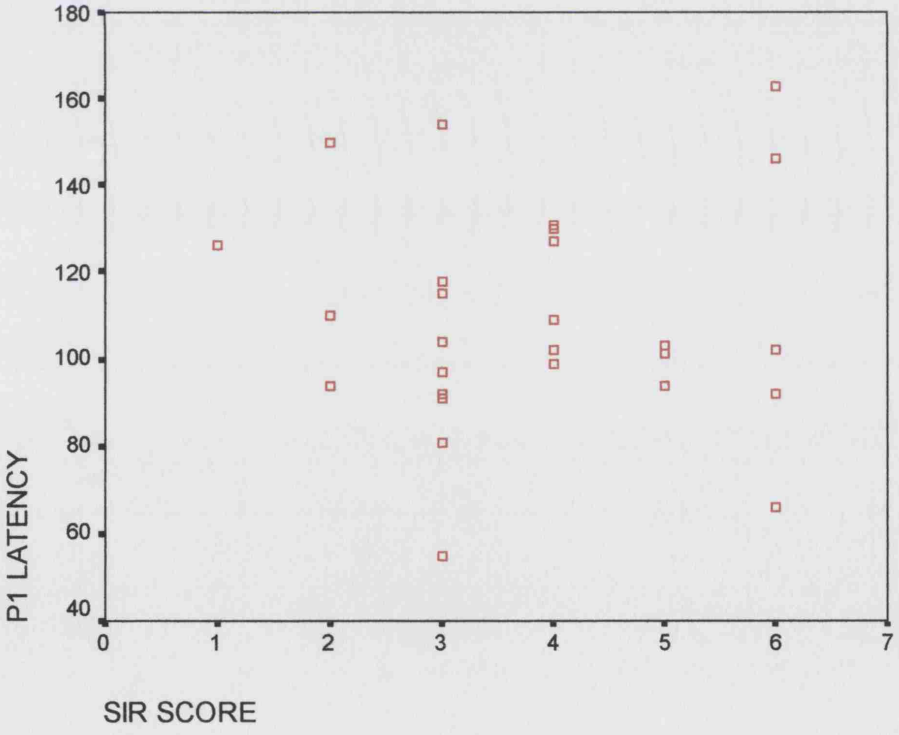

Figure 20 B: P1 latency (ms) vs Speech intelligibility rating (SIR) score

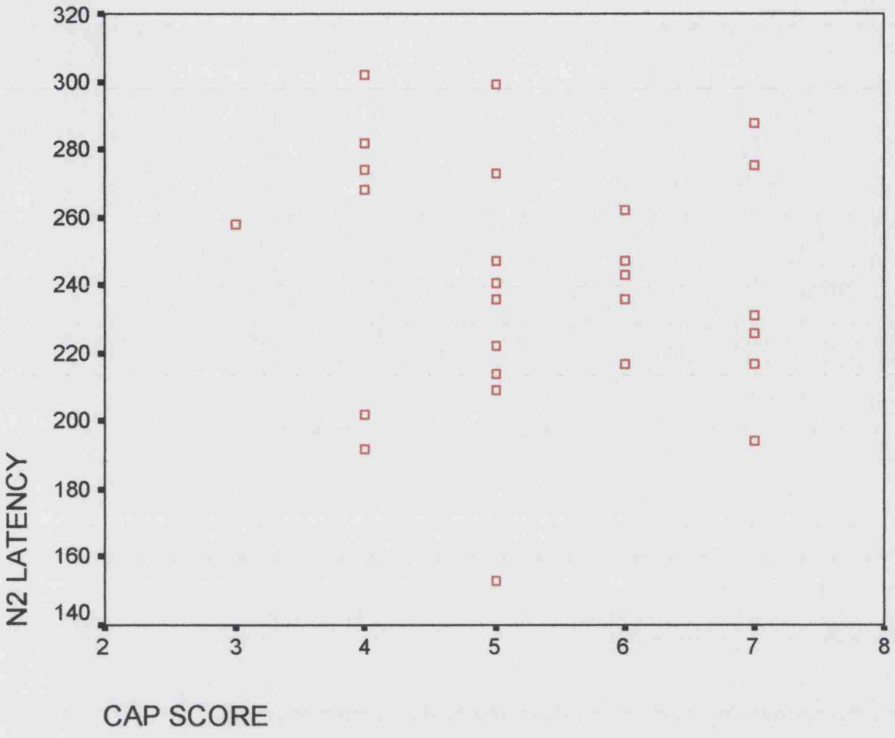

Figure 20 C: N2 latency (ms) vs Category of auditory performance (CAP) score

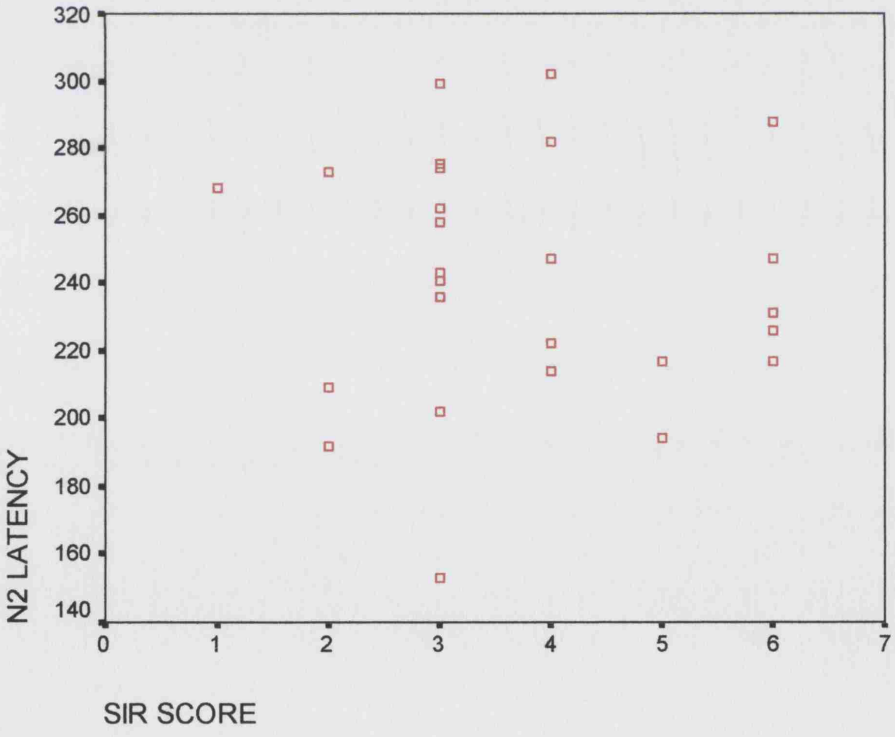

Figure 20 D: N2 latency (ms) vs Speech intelligibility rating (SIR) score

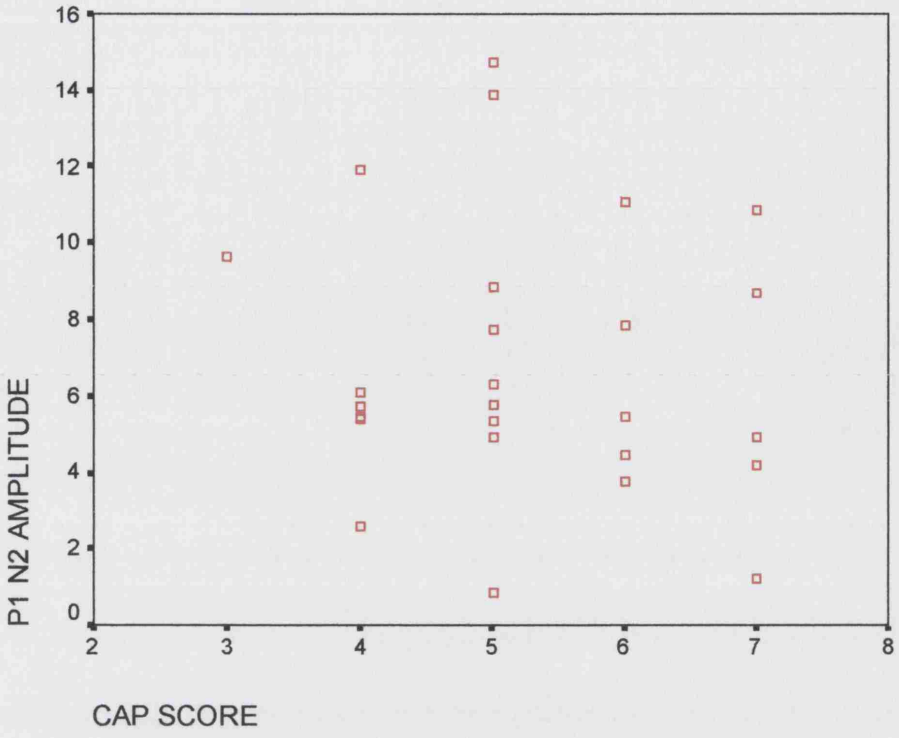

Figure 20 E: P1 N2 amplitude (μV) vs Category of auditory performance (CAP) score

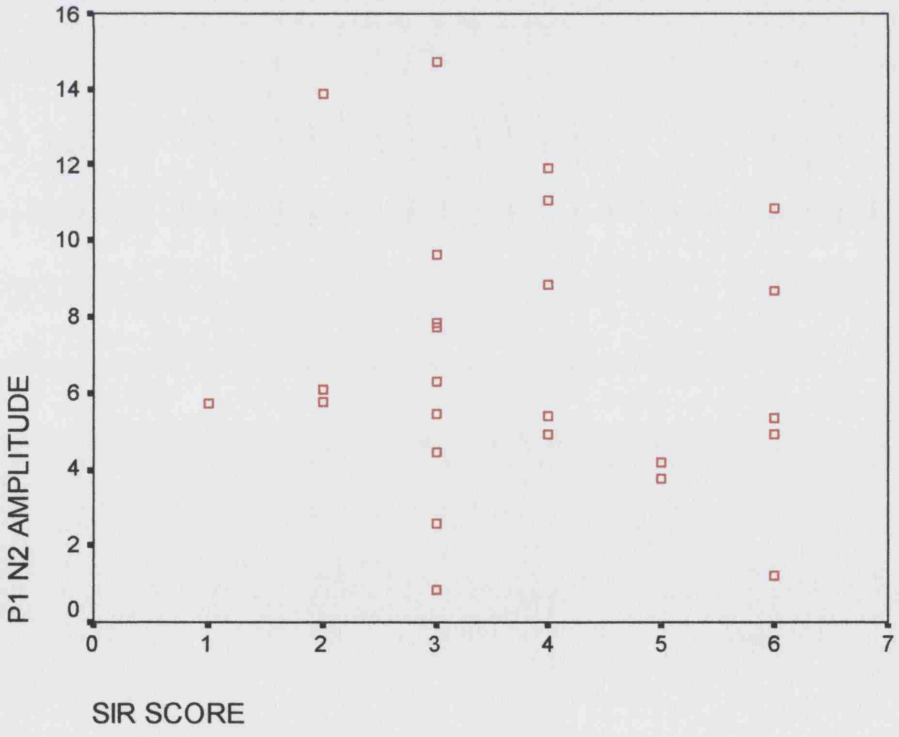

Figure 20 F: P1 N2 amplitude (μV) vs Speech intelligibility rating (SIR) score

Bi-variate correlation analysis assessing the relationship between latency of P1 and age of the patient did not reveal any relationship (Figure 20 H). A similar analysis assessing the relationship of P1 latency with duration of implant use (time in sound) revealed a negative linear trend which was statistically significant. (Pearson's correlation = -.45, P=0.01, Slope= - 3.65, Regression equation: P1 latency = 130.88 - (3.65 X Duration of implant use) Latency of P1 reduced by 3.65 ms for every one year of use of an implant (Figure 20 G). Similar analysis carried out for N2 latency and P1-N2 amplitude did not reveal any significant relationship (Figures 20 I-L).

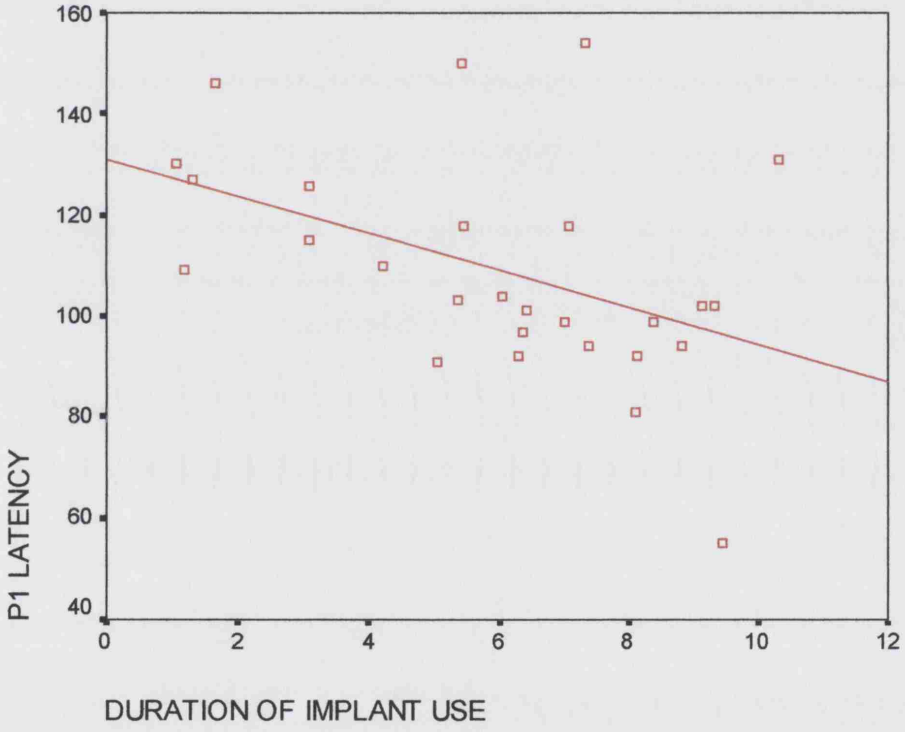

Figure 20 G: P1 latency (ms) vs duration of implant use (years) in pre-lingual deaf patients. (Pearson's correlation = -0.45, p=0.01)

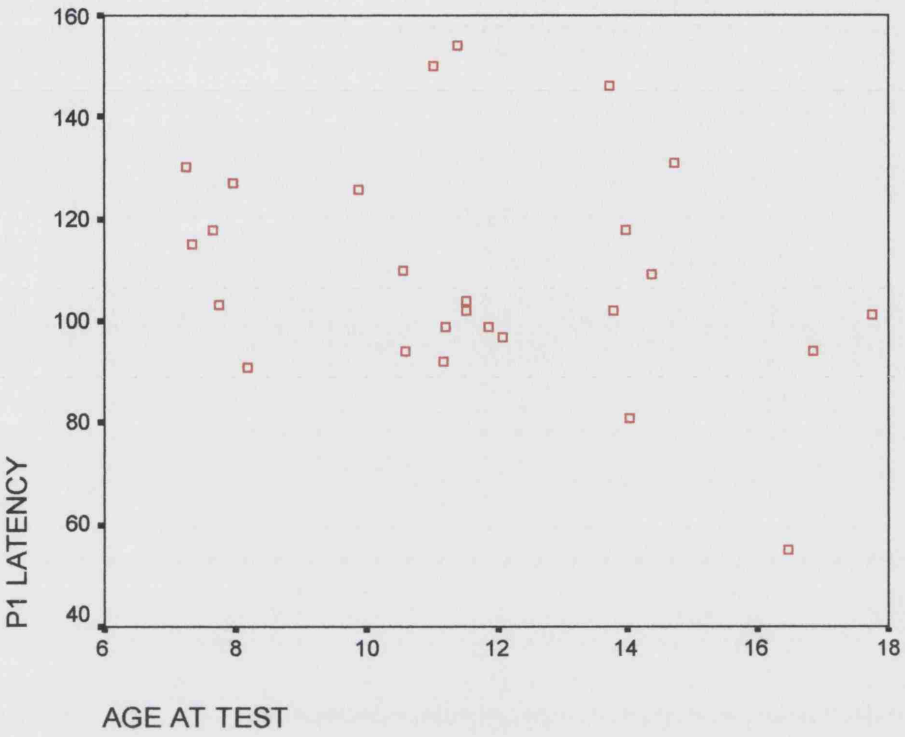

Figure 20 H: P1 latency (ms) vs age of the patient (years).

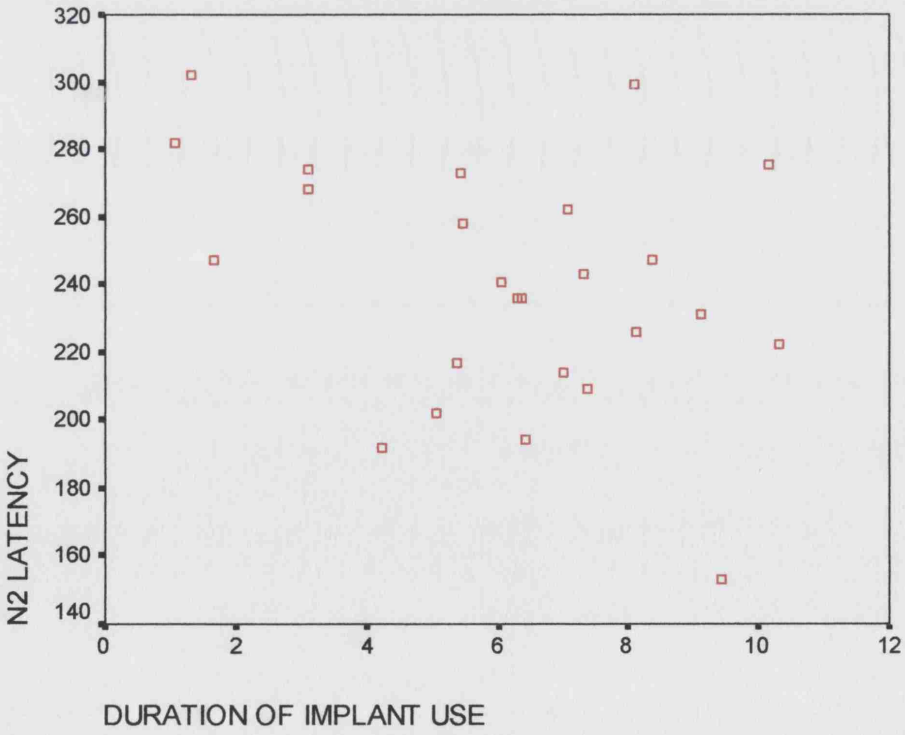

Figure 20 I: N2 latency (ms) vs duration of implant use (years)

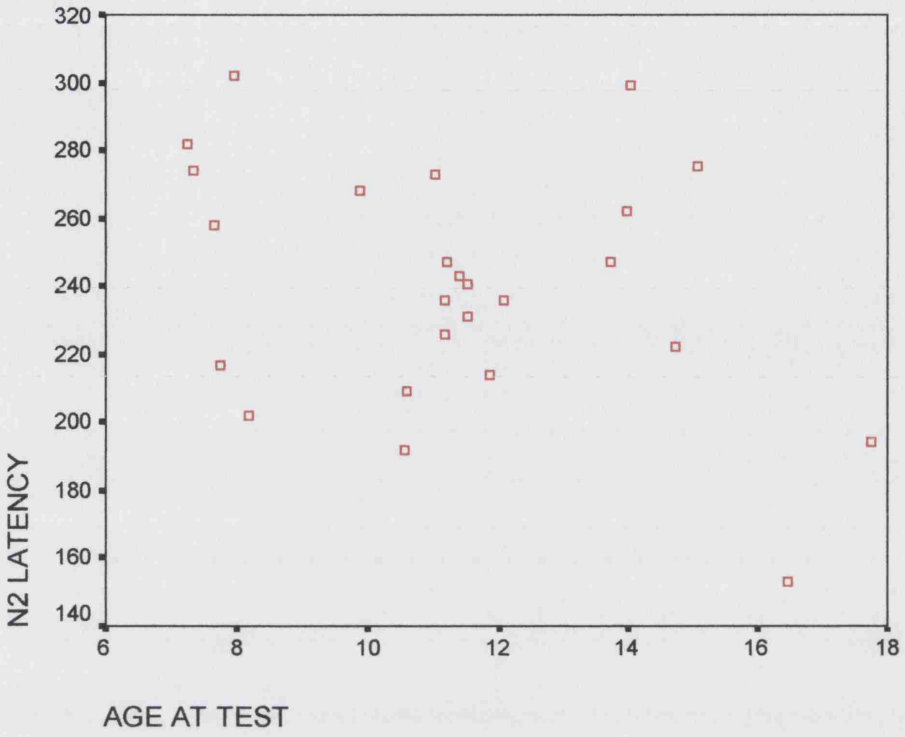

Figure 20 J: N2 latency (ms) vs age of the patient (years)

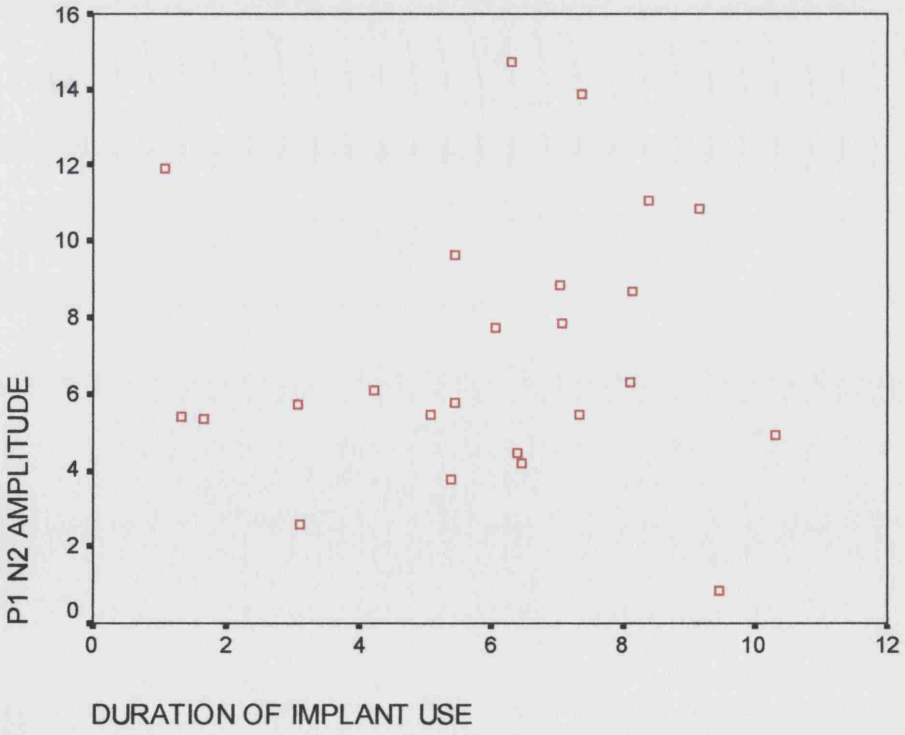

Figure 20 K: P1 N2 amplitude (μV) vs duration of implant use (years)

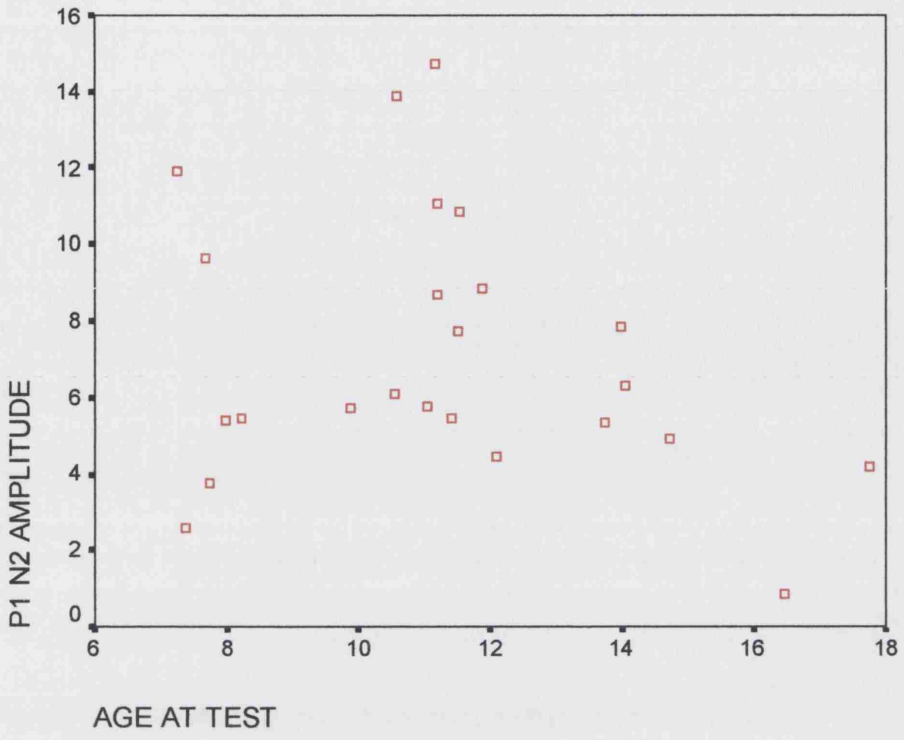

Figure 20 L: P1 N2 amplitude (μV) vs age of the patient (years)

Bi-variate correlation analysis assessing the relationship between latency and amplitude of P1 and N2 components and age of implantation in the pre-lingual group did not reveal any statistically significant results (Figures 20M – P).

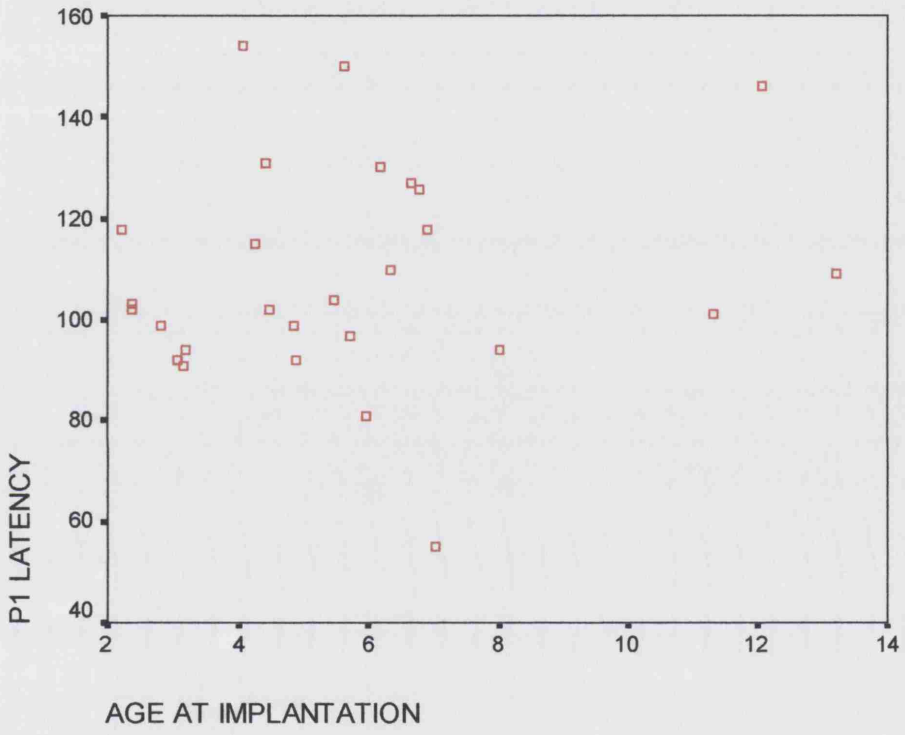

Figure 20 M: P1 latency (ms) vs age at implantation (years)

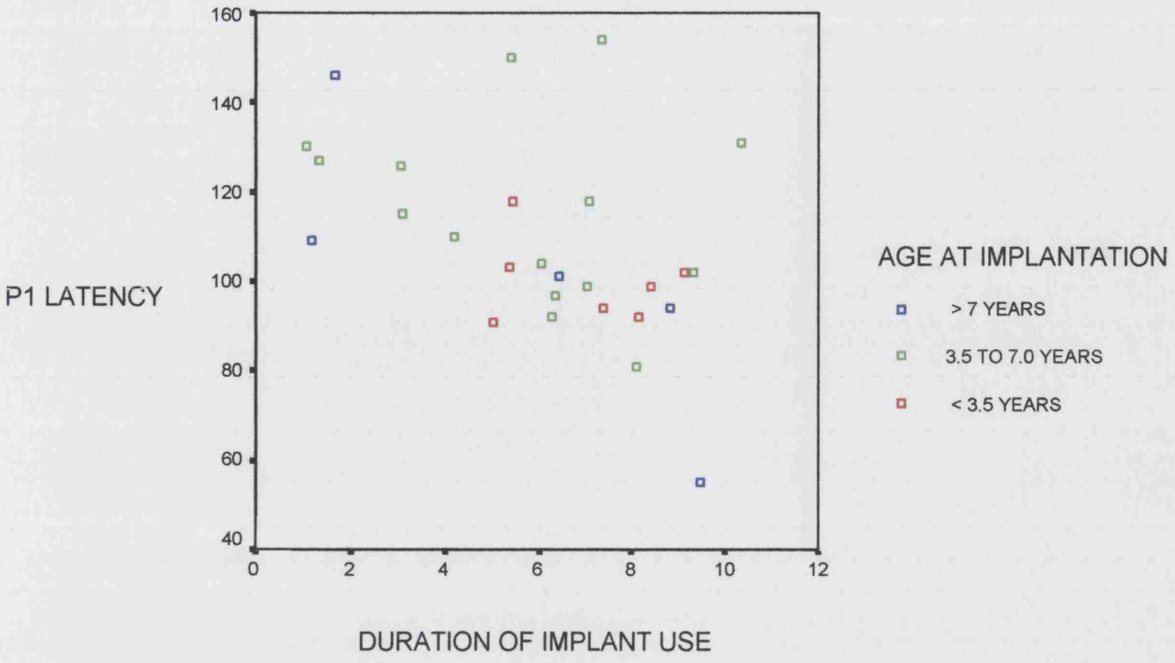

Figure 20 N: P1 latency (ms) vs duration of implant use (years) - illustrating distribution of patients based on age at implantation. No difference is apparent in the maturational trend of P1 latency with use of implant in between the three groups (>7 years, 3.5 – 7 years, <3.5 years).

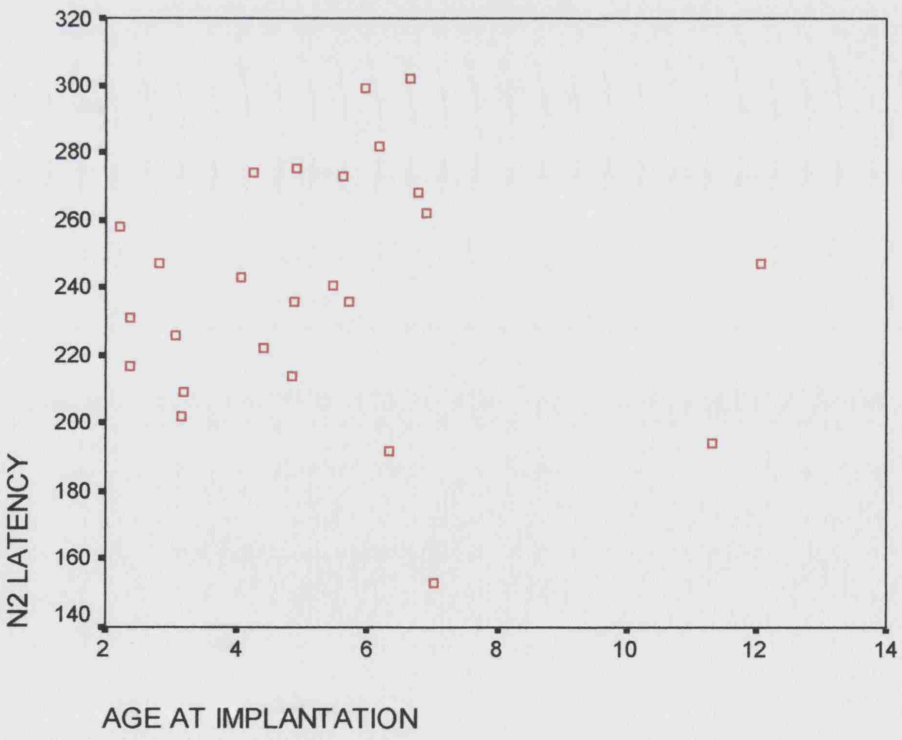

Figure 20 O: N2 latency (ms) vs age at implantation (years)

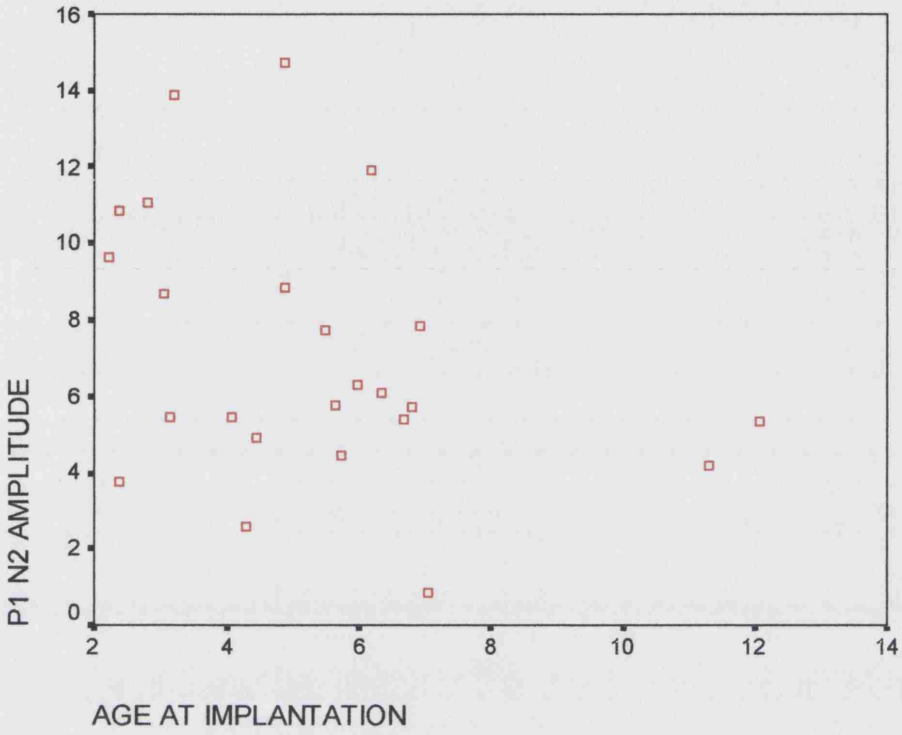

Figure 20 P: P1 N2 amplitude (μV) vs age at implantation (years)

5.2 MISMATCH NEGATIVITY

MMN was identified in 10 of the 35 patients recorded in our study. The MMN had a mean peak latency of 267±62 ms, mean onset latency of 168±61 ms and amplitude (peak to peak) of 4.7±1.4μV (Table VI).

Patient No.	CAP Score	Aetiology	SIR Score	Peak Latency (ms)	Onset latency (ms)	Amplitude (μV)	Duration (ms)
1	7	Acquired	5	226	189	1.98	128
2	7	Post-lingual	6	261	76	6.04	384
3	7	Post-lingual	6	279	101	3.45	377
4	7	Congenital	3	162	113	5.88	144
5	7	Acquired	5	396	212	7.26	219
7	7	Congenital	6	271	216	4.19	187
23	5	Congenital	6	214	117	4.91	342
24	5	Congenital	2	255	184	5.12	139
26	5	Congenital	4	286	229	3.97	200
30	4	Acquired	3	320	250	4.54	111
			MEAN	267	168.7	4.73	223.1
			SD	62.95	61.42	1.48	105.67

Table VI: ERP measures in cochlear implant patients who evoked MMN

Pearson's chi square analysis revealed a trend of CAP score (7, 6, 5, </=4) and presence of MMN (Pearson's chi-square=15.2, P=0.002) with those patients with a higher CAP score revealing an MMN in comparison to those with a lower CAP score who did not (Tables VII, VIII). Further analysis investigating the presence or absence of MMN and SIR score (6, 5, 4, </=3) also revealed a similar trend. (Pearson chi-square=11.14, P=0.01). These trends were supported using Fishers exact probability test (CAP: 7 vs $\leq$ 6, P=0.001; SIR: 6 vs $\leq$ 5, P=0.017).

CAP	MMN Present (%)	MMN Absent
7	6(85.7)	1
6	0	7
5	3(25)	10
<=4	1(12.5)	7
	Pearson chi-square=15.2, P= 0.002	

Table VII: Pearson's chi-square analysis of presence or absence of MMN based on CAP score

SIR	MMN Present (%)	MMN Absent
6	4(80)	1
5	2(66.6)	1
4	1(12.5)	7
<=3	3(15.7)	16
	Pearson chi-square =11.14, P= 0.011	

Table VIII: Pearson's chi-square analysis of presence or absence of MMN based on SIR score

In the grand averages of patients with a CAP score of 7 (star performers) an MMN was clearly evident in the frontal and central electrode positions, with a peak latency of 267 ms. (Figure 23 B,C). The onset time was 127 msec and offset time was 375 msec. Grand averages of patients with a CAP score of </=5 revealed no MMN (Figure 23 D,E)

Investigation of the symmetry of responses over frontal and central electrodes revealed no significant differences in the peak latency, duration and amplitude measures of MMN between the right and left electrode sites [C3 compared to C4 (Latency: t=-0.17, P=0.86, Duration: t=2.37, P=0.55, Amplitude: t=0.77, P=0.47) and F3 compared to F4 (Latency: t=1.32, P=0.22, Duration: t=-0.64, P=0.54, Amplitude: t=-2.1, P=0.08)].

The outcome of bi-variate correlation analysis carried out to assess the relationship of MMN (peak and onset latency, amplitude, area and duration measures) with behavioural assessment measures (CAP and SIR scores) revealed no significant correlation between latency, amplitude and area measures and behavioural scores (Figure 21 C-J). However the duration of MMN demonstrated a significant positive linear correlation with the SIR score (Pearson's correlation=0.73, P=0.01, Slope=51.73) (Figure 21 A-B).

MMN parameters (duration, onset latency, peak latency, and amplitude) across all behavioural groups is detailed in Table IX.

In pre-lingually deaf children, bi-variate correlation analysis assessing the relationship between MMN (amplitude, duration, area and latency) and age of the patient / duration of implant use did not reveal any significant relationship (Figure 21 K-P).

	Duration of MMN	Amplitude of MMN	Onset latency of MMN	Peak latency of MMN
		Mean ± SD		
CAP 7 n=6	239.8 ± 113.5	4.7 ± 1.9	151.1 ± 61.5	265.8 ± 76.8
CAP 6 n=0				
CAP 5 n=3	227 ± 104.1	4.6 ± 0.6	176.6 ± 56.3	251.6 ± 36.1
CAP <=4 n=1	111 .	4.54 .	250 .	320 .
SIR 6 n=4	322.5 ± 92.1	4.6475 ± 1.1	127.5 ± 61.3	256.2 ± 29.1
SIR 5 n=2	173.5 ± 64.3	4.6195 ± 3.7	200.5 ± 16.2	311 ± 120.2
SIR 4 n=1	200 .	3.97 .	229 .	286 .
SIR<=3 n=3	131.3 ± 17.7	5.1 ± 0.6	182.3 ± 68.5	245.6 ± 79.4

Table IX: Onset and peak latency, duration and amplitude of MMN in different behavioural groups based on CAP and SIR score

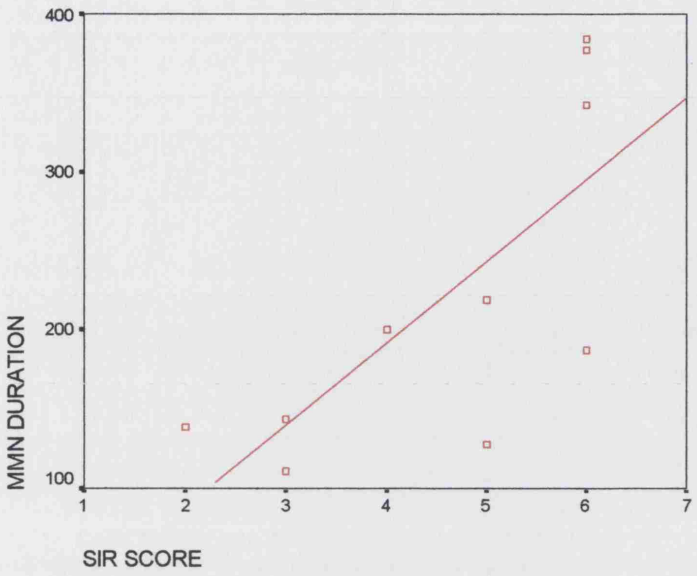

Figure 21A: MMN duration (ms) vs Speech intelligibility rating (SIR) score (Pearson's correlation=0.73, P=0.01, Slope=51.73 ; *Spearman correlation=0.73, P=0.01*)

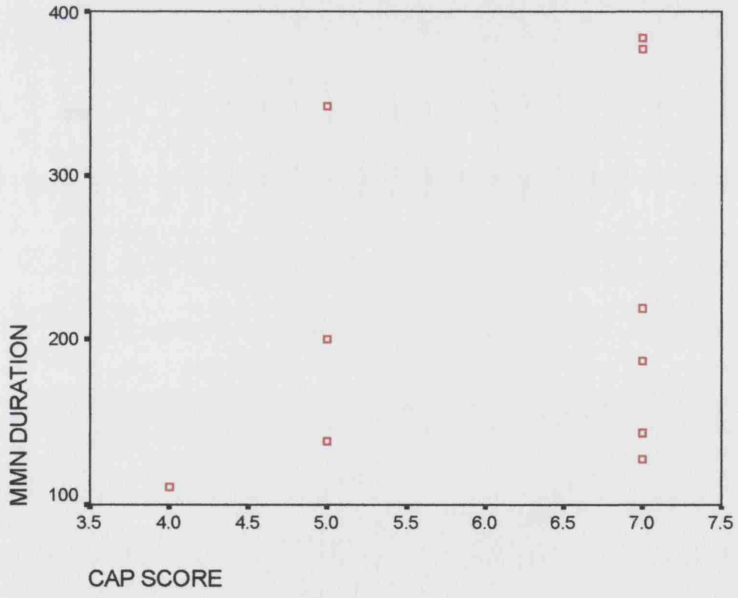

Figure 21 B: MMN duration (ms) vs Category of auditory performance (CAP) score

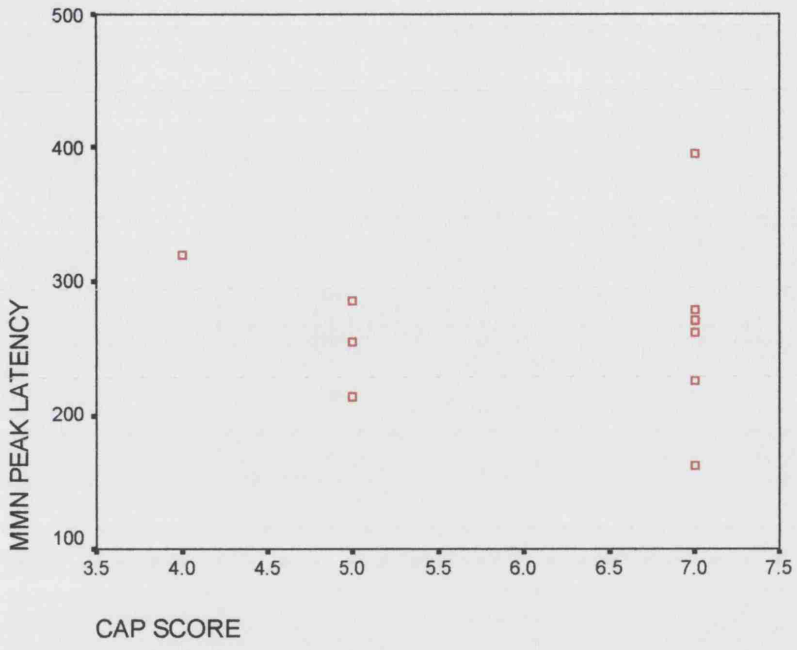

Figure 21 C: MMN peak latency (ms) vs Category of auditory performance (CAP) score

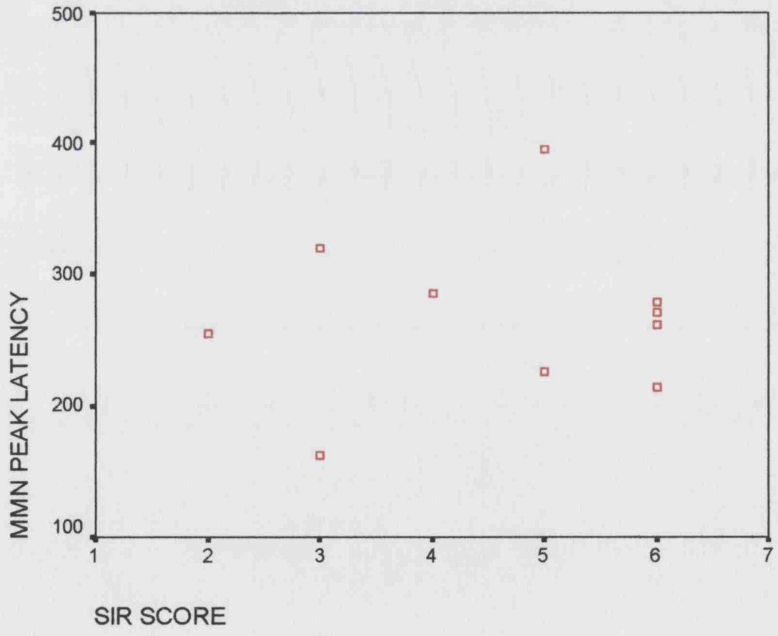

Figure 21 D: Mismatch negativity (MMN) peak latency (ms) vs Speech intelligibility rating (SIR) score

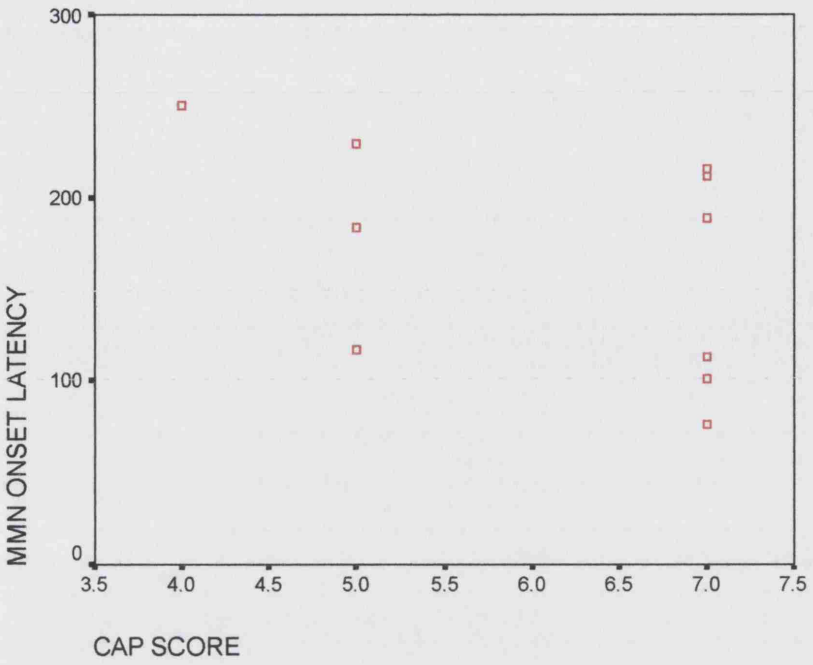

Figure 21 E: Mismatch negativity (MMN) onset latency (ms) vs CAP score

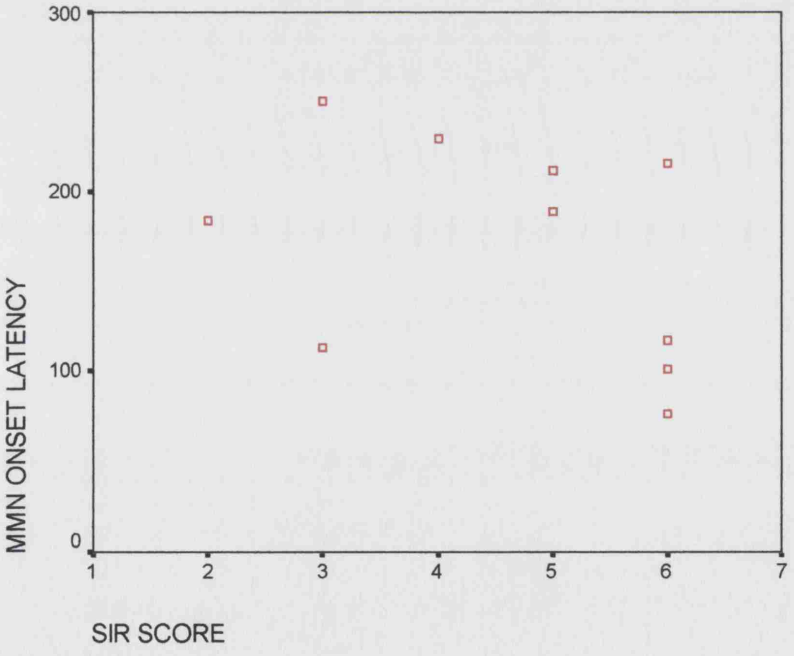

Figure 21 F: Mismatch negativity (MMN) onset latency (ms) vs SIR score

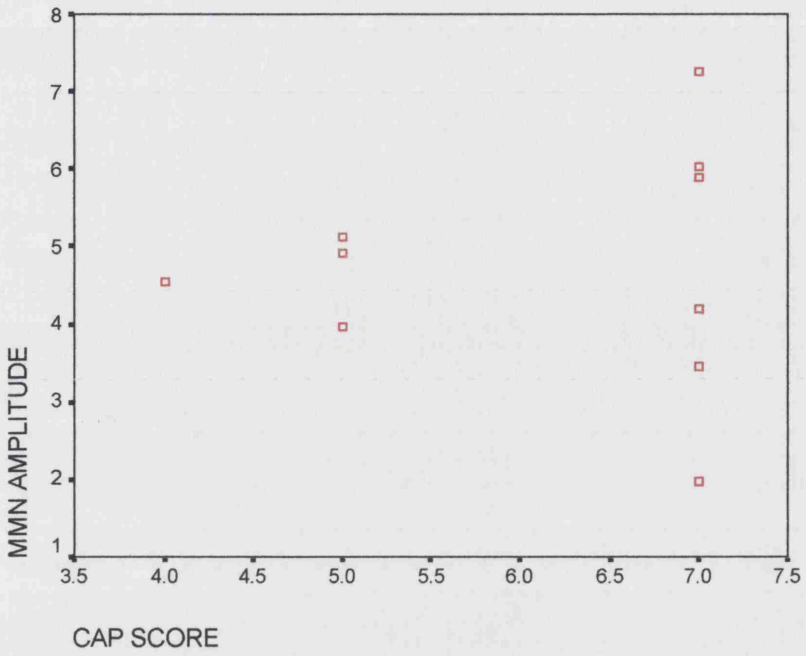

Figure 21 G: Mismatch negativity (MMN) amplitude (μV) (peak to peak) vs CAP score

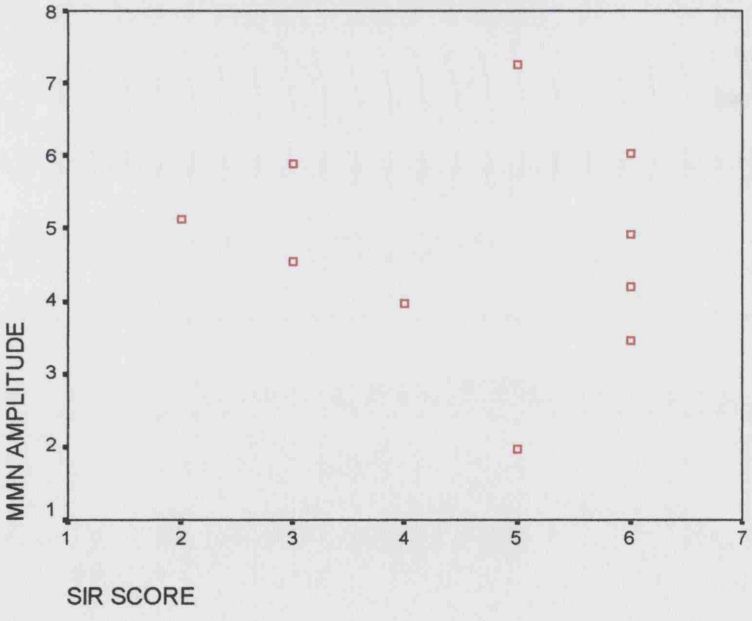

Figure 21 H: Mismatch negativity (MMN) amplitude (μV) (peak to peak) vs Speech intelligibility rating (SIR) score

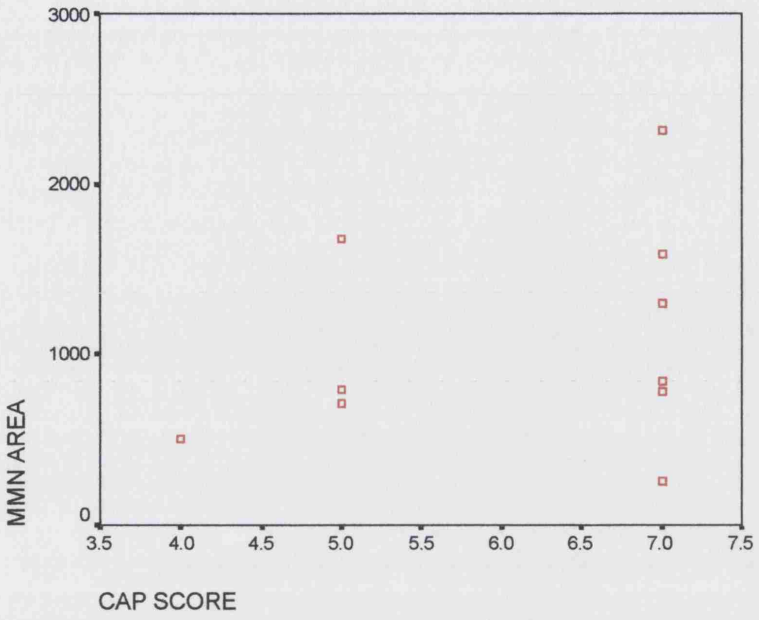

Figure 21 I: Mismatch negativity (MMN) area (duration X amplitude) vs Category of auditory performance (CAP) score

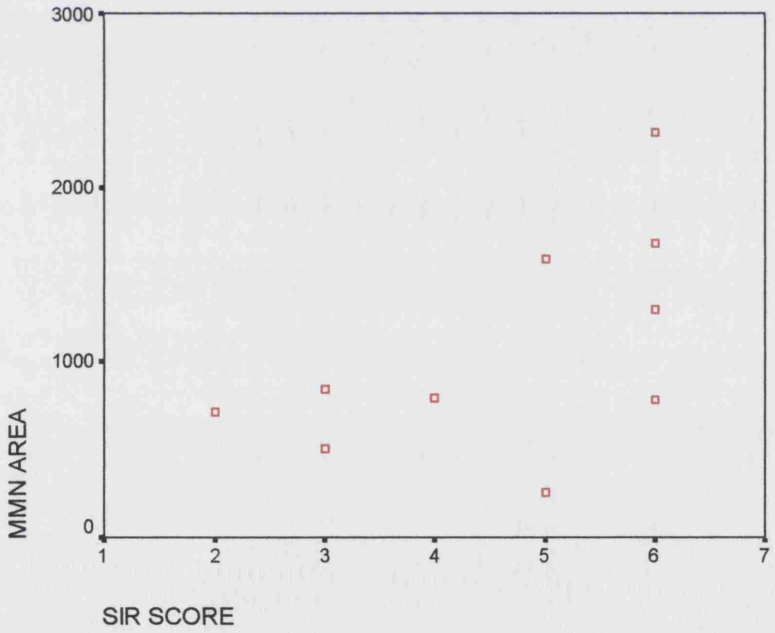

Figure 21 J: Mismatch negativity (MMN) area (duration X amplitude) vs Speech intelligibility (SIR) score

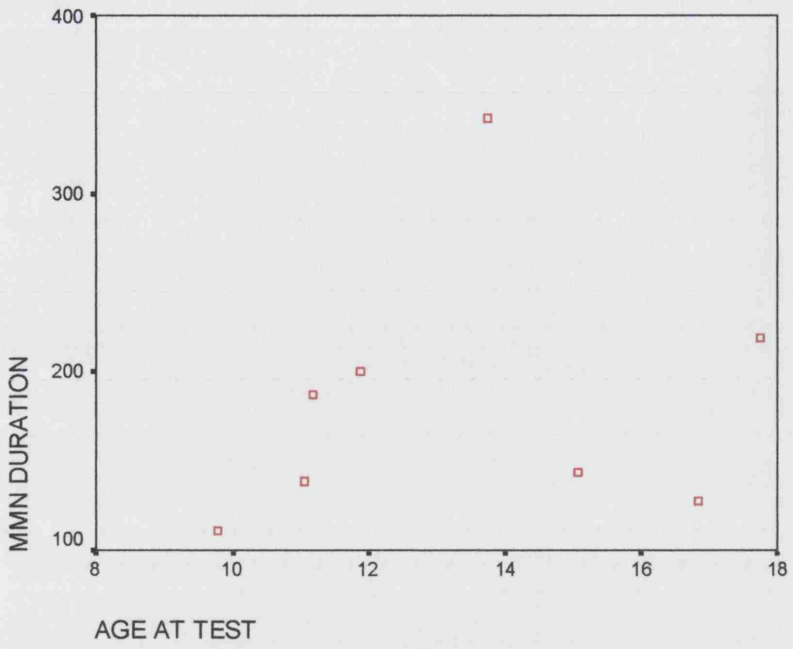

Figure 21 K: Mismatch negativity (MMN) duration (ms) vs age at test (years)

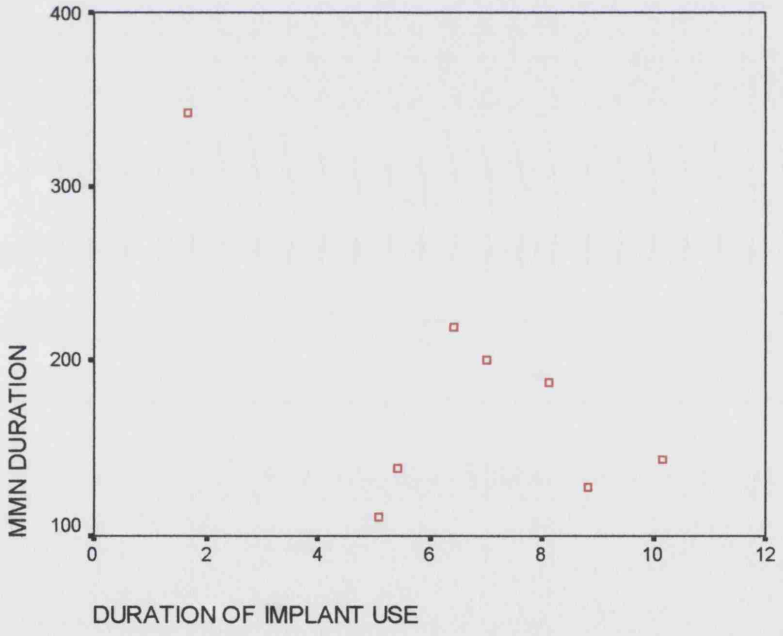

Figure 21 L: Mismatch negativity (MMN) duration (ms) vs duration of implant use (years)

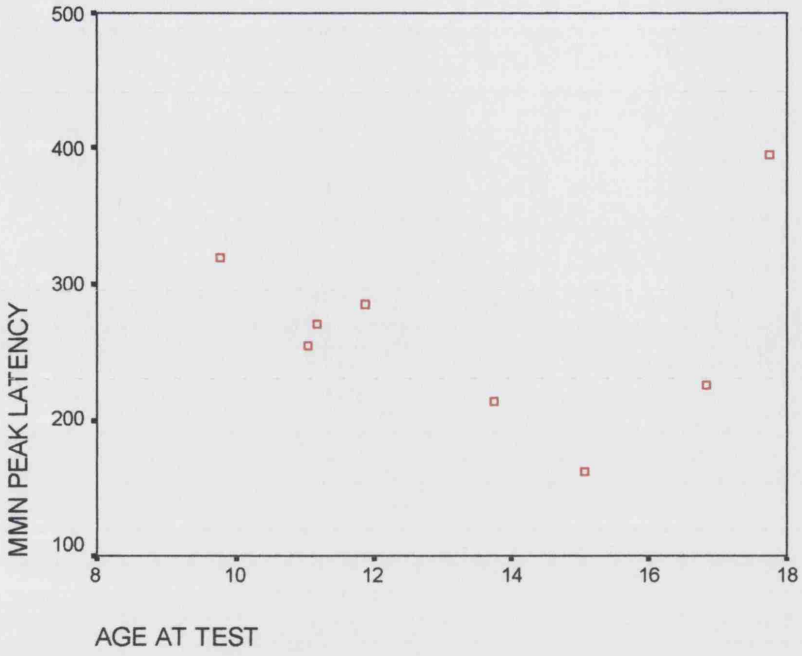

Figure 21 M: Mismatch negativity (MMN) peak latency (ms) vs age at test (years)

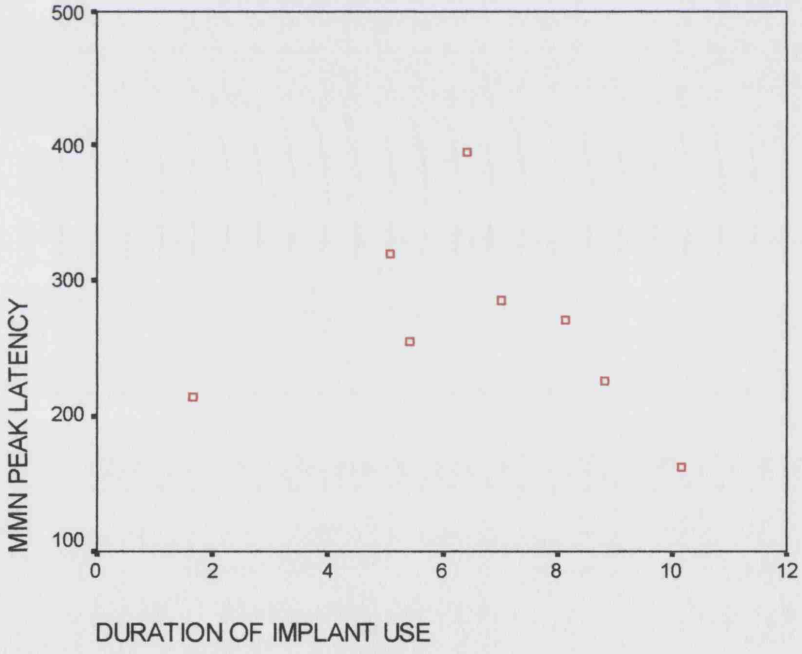

Figure 21 N: Mismatch negativity (MMN) peak latency (ms) vs duration of implant use (years)

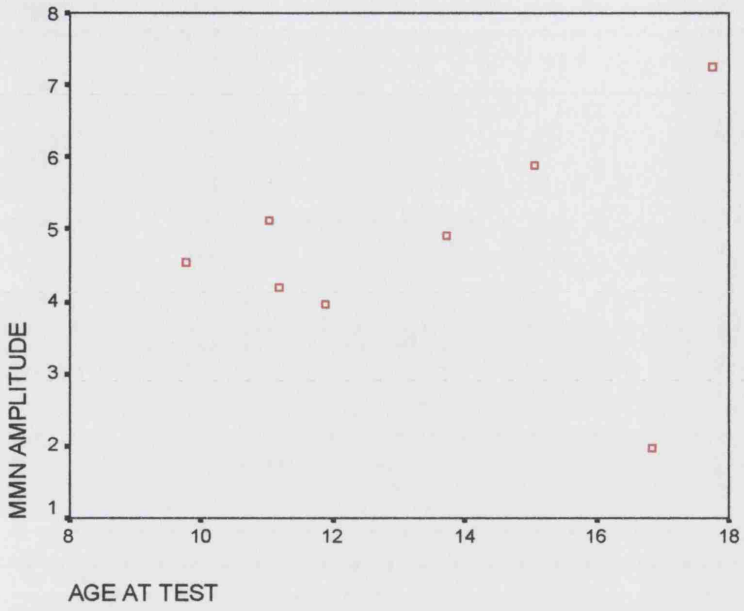

Figure 21 O: Mismatch negativity (MMN) peak to peak amplitude (μV) vs age at test (years)

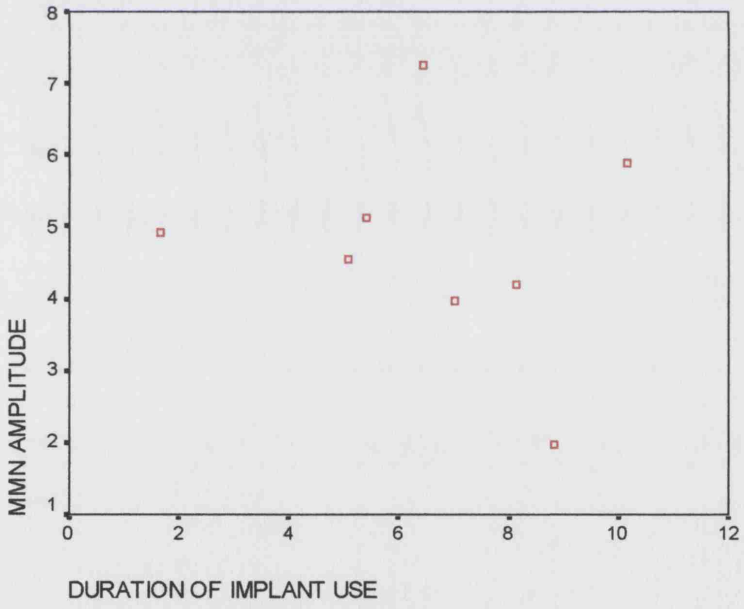

Figure 21 P: Mismatch negativity (MMN) peak to peak amplitude (μV) vs duration of implant use (years)

Bi-variate correlation analysis assessing the relationship between latency, amplitude and duration of MMN and age of implantation in the pre-lingual group did not reveal any statistically significant results (Figures 21 Q - S).

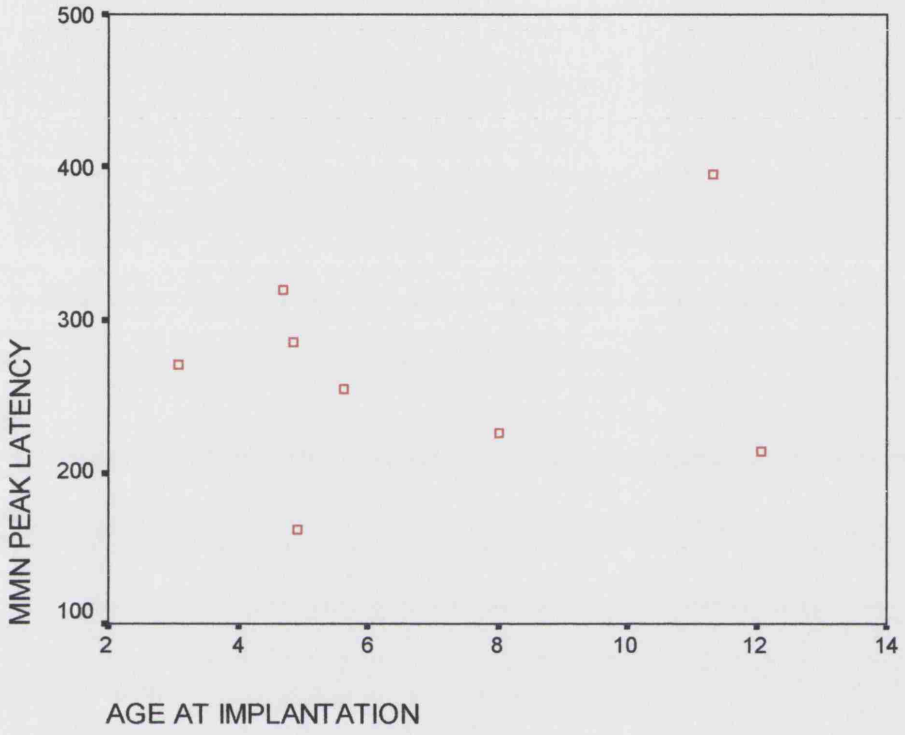

Fig 21 Q: Mismatch negativity (MMN) peak latency (ms) vs age at implantation (years)

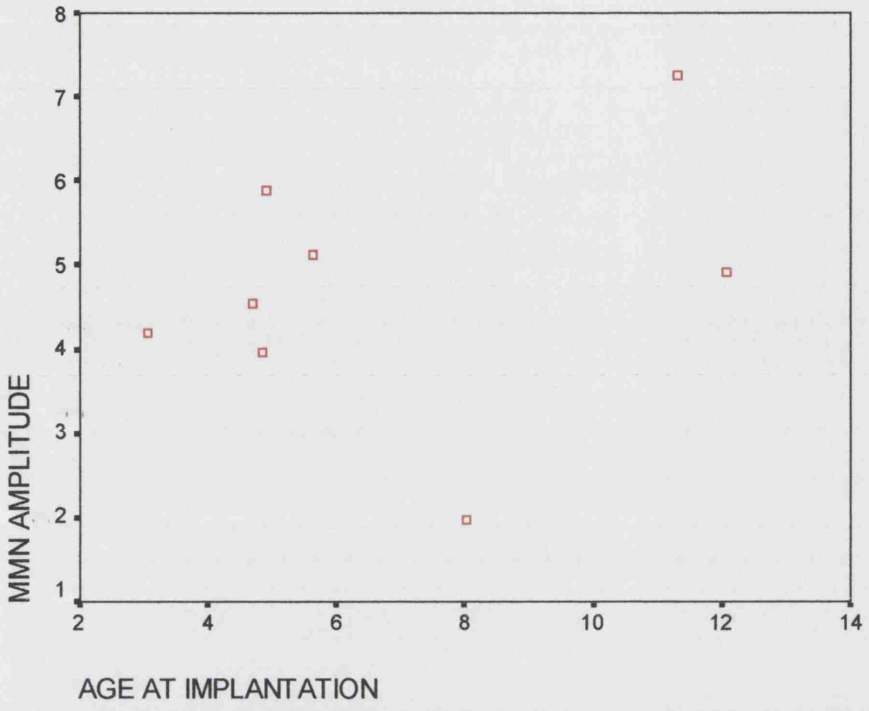

Figure 21 R: Mismatch negativity (MMN) amplitude (μV) vs age at implantation (years)

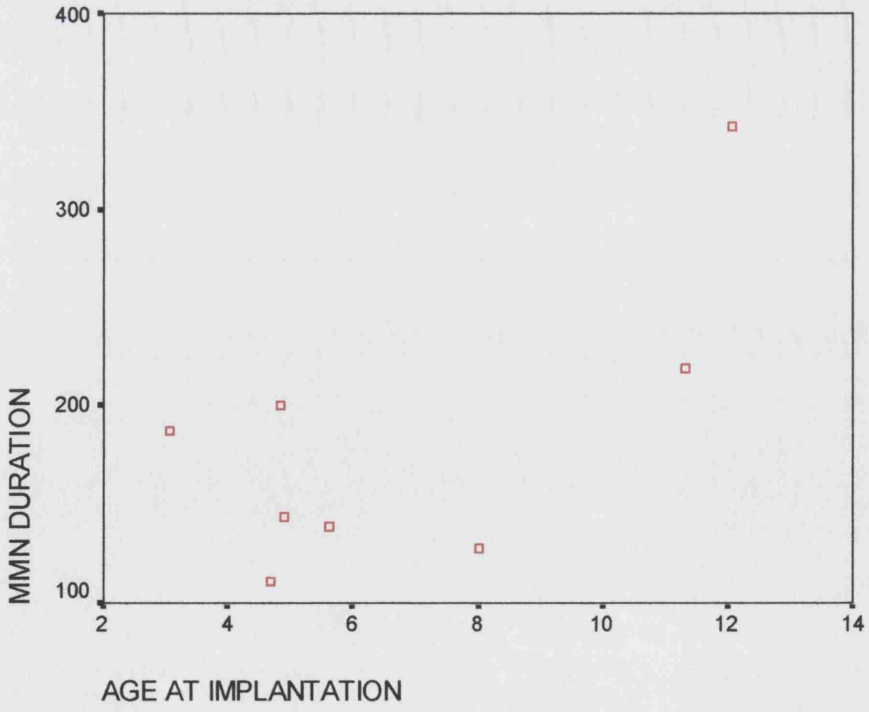

Figure 21 S: Mismatch negativity (MMN) duration (ms) vs age at implantation (years)

5.3 LATE DISCRIMINATIVE NEGATIVITY (LDN):

LDN was identified in 14 of the 35 patients recorded in our study. The LDN had a mean peak latency of 701.7 $\pm$ 79.5 ms. , mean onset latency of 571.4 $\pm$ 97.2 ms and amplitude (peak to peak) of 5.6$\pm$2.1μV.

Pearson's chi square analysis did not reveal any trend of CAP / SIR score and presence or absence of LDN.

In the grand averages of patients with a CAP score of 5 and below (poor performers) an LDN was clearly evident in the frontal and central electrode positions, with a peak latency of 701 ms. Grand averages of patients with a CAP score of 7 revealed no LDN (Figure 24). LDN parameters (latency, amplitude and duration across different behavioural groups is detailed in Table X)

The outcome of bi-variate correlation analysis carried out to assess the relationship of LDN (peak and onset latency, amplitude, area and duration measures) with behavioural assessment measures (CAP and SIR scores) revealed no significant correlation between amplitude, latency, and area measures and behavioural scores (Figure 22 E-F) . The duration of LDN demonstrated a significant negative linear correlation with the CAP (Pearson's correlation= - 0.72, P=0.003) and SIR score (Pearson's correlation= - 0.64, P=0.01) (Figure 22 A-B).

In pre-lingually deaf children, bi-variate correlation analysis assessing the relationship between LDN (amplitude, duration, area and latency) and age of the patient / duration of implant use did not reveal any significant relationship (Figure 22 G-L).

	Duration of LDN	Amplitude of LDN	Onset latency of LDN	Peak latency of LDN
		MEAN ± SD		
CAP 7 n=3	125.6 ± 11.2	3.9 ± 0.6	710.0 ± 76.2	776.6 ± 63.3
CAP 6 n=1	249 .	4.4 .	554 .	645 .
CAP 5 n=5	267.0 ± 62.6	5.6 ± 2.8	542.0 ± 74.5	703.4 ± 76.8
CAP <=4 n=5	282.4 ± 63.0	7.0 ± 1.3	521.2 ± 59.8	666.4 ± 77.7
SIR 6 n=3	181.3 ± 107.1	5.0 ± 1.9	676.0 ± 134.7	772.6 ± 70.2
SIR 5 n=1	138.0 ± .	3.8 ± .	623.0 ± .	704.0 ± .
SIR 4 n=3	230.6 ± 15.8	5.0 ± 1.4	554.0 ± 19.0	673.0 ± 55.5
SIR<=3 n=7	285.5 ± 64.3	6.5 ± 2.5	526.7 ± 77.0	683.2 ± 87.7

Table X: Onset and peak latency, duration and amplitude of LDN in different behavioural groups based on CAP and SIR score.

Figure 22 A: Late discriminative negativity (LDN) duration (ms) vs Speech intelligibility rating (SIR) score (Pearson's correlation = -0.64, P=0.01)

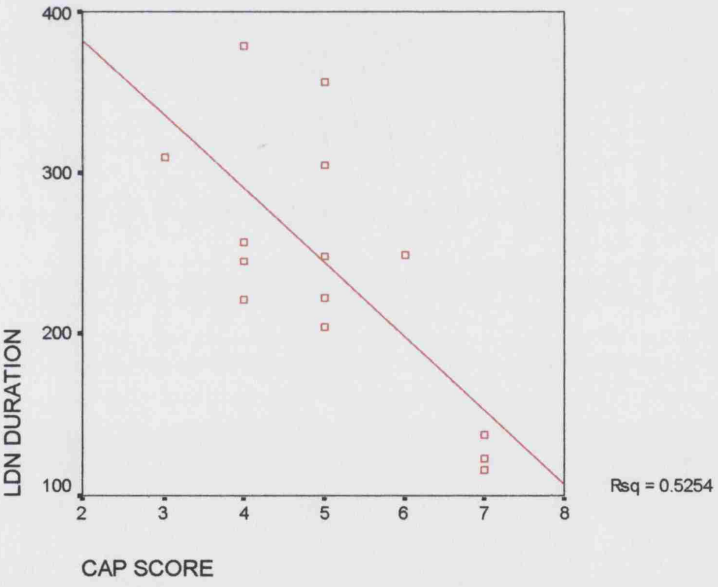

Figure 22 B: Late discriminative negativity (LDN) duration (ms) vs Category of auditory performance (CAP) score (Pearson's correlation = -0.72, P=0.003)

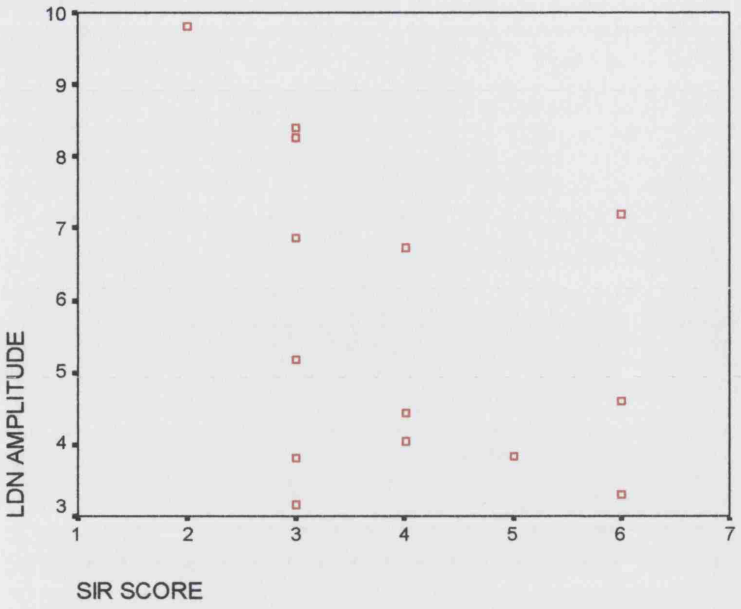

Figure 22 C: Late discriminative negativity (LDN) amplitude (μV) vs Speech intelligibility rating (SIR) score

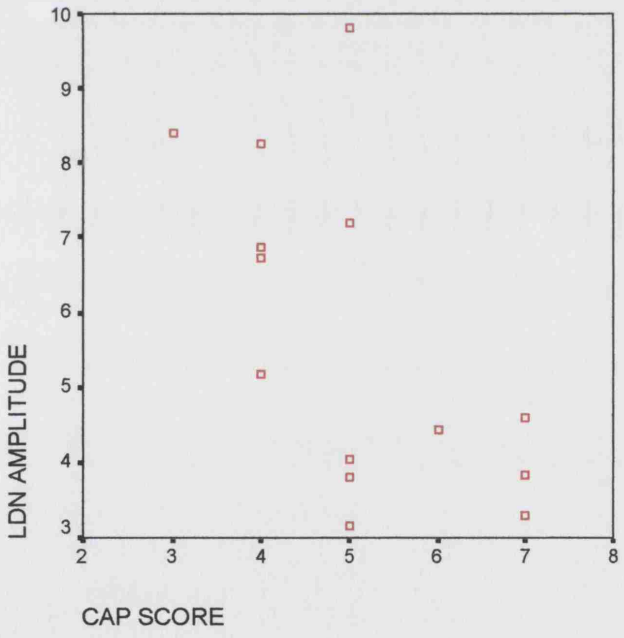

Figure 22 D: Late discriminative negativity (LDN) amplitude (μV) vs Category of auditory performance score (CAP) score

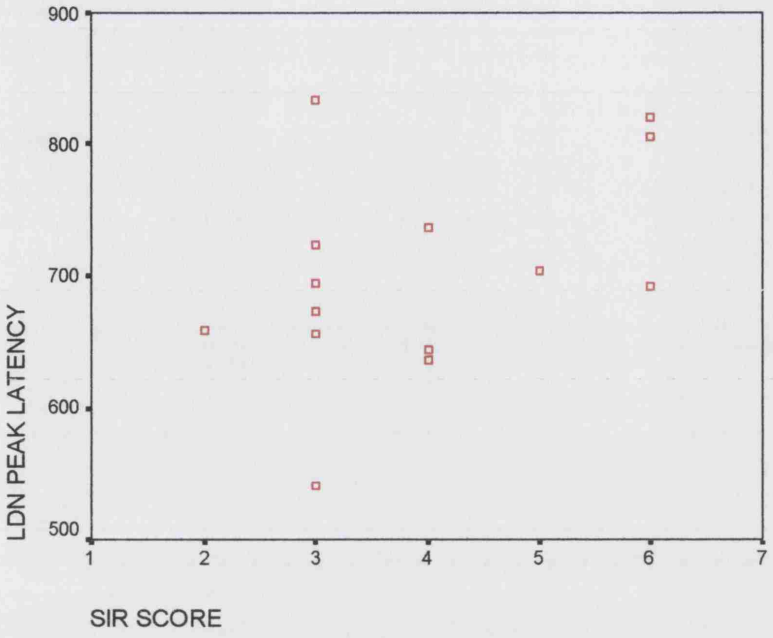

Figure 22 E: Late discriminative negativity (LDN) peak latency (ms) vs Speech intelligibility rating (SIR) score

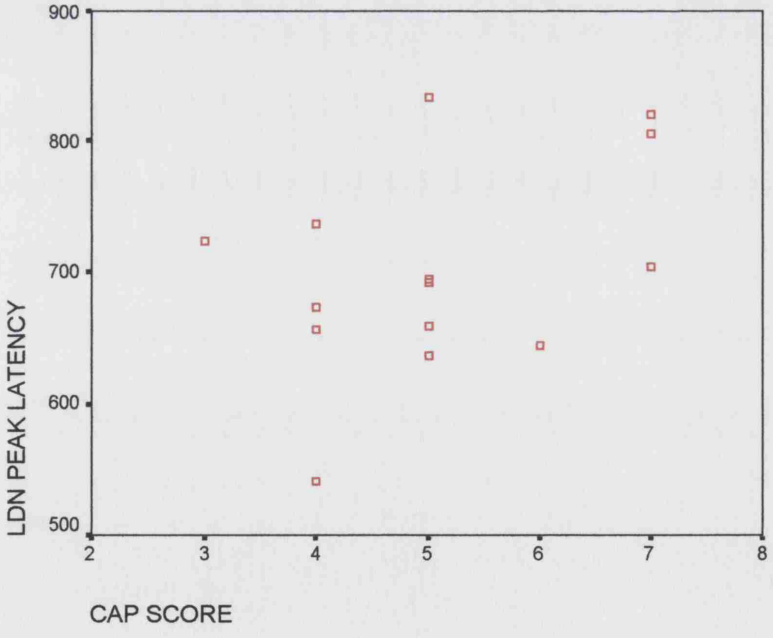

Figure 22 F: Late discriminative negativity (LDN) peak latency (ms) vs Category of audit performance CAP score

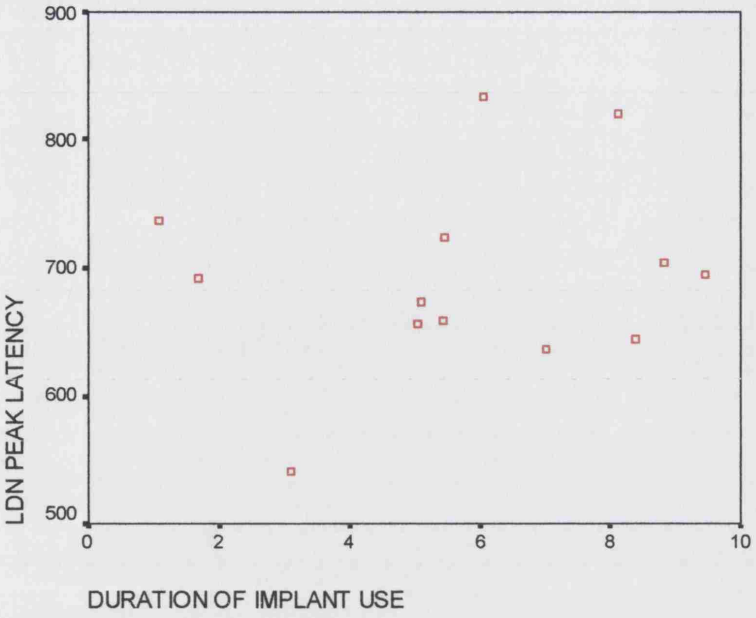

Figure 22 G: Late discriminative negativity (LDN) peak latency (ms) vs duration of implant use (years)

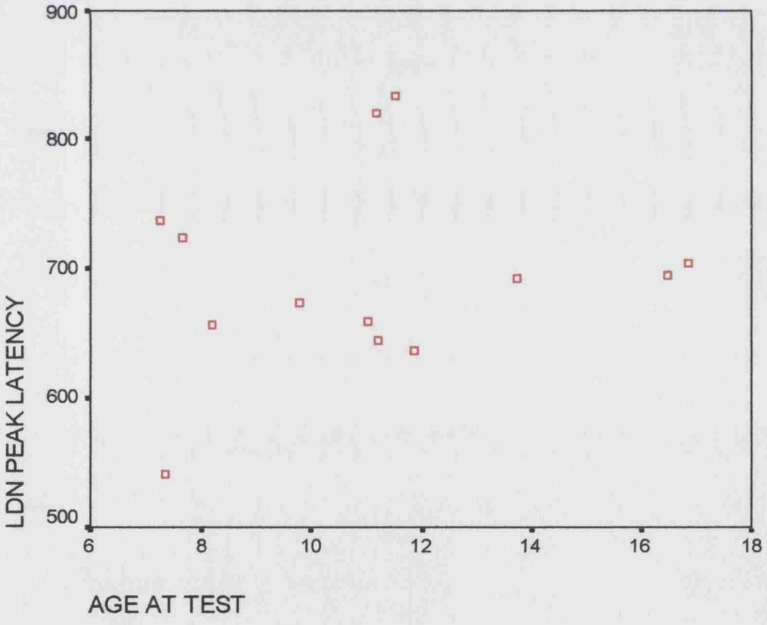

Figure 22 H: Late discriminative negativity (LDN) peak latency (ms) vs age at test (years)

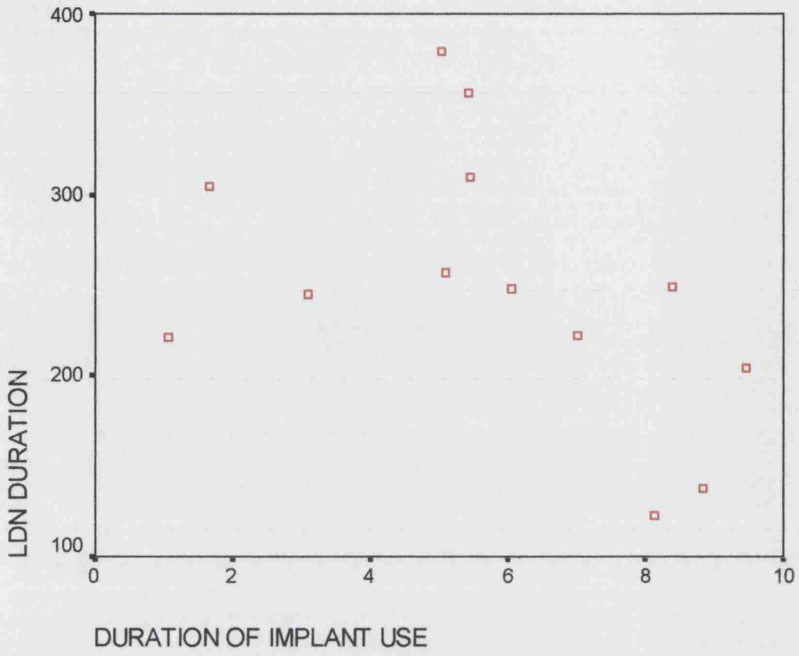

Figure 22 I: Late discriminative negativity (LDN) duration (ms) vs duration of implant use (years)

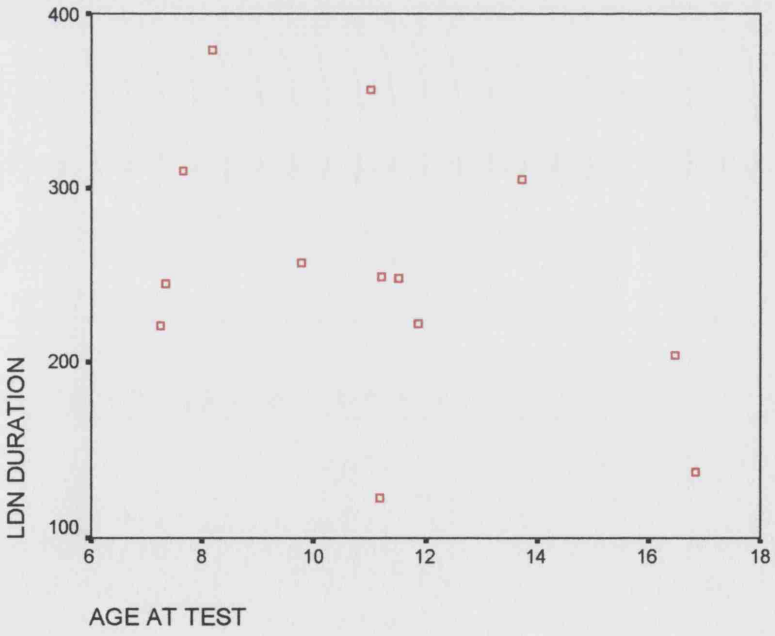

Figure 22 J: Late discriminative negativity (LDN) duration (ms) vs age at test (years)

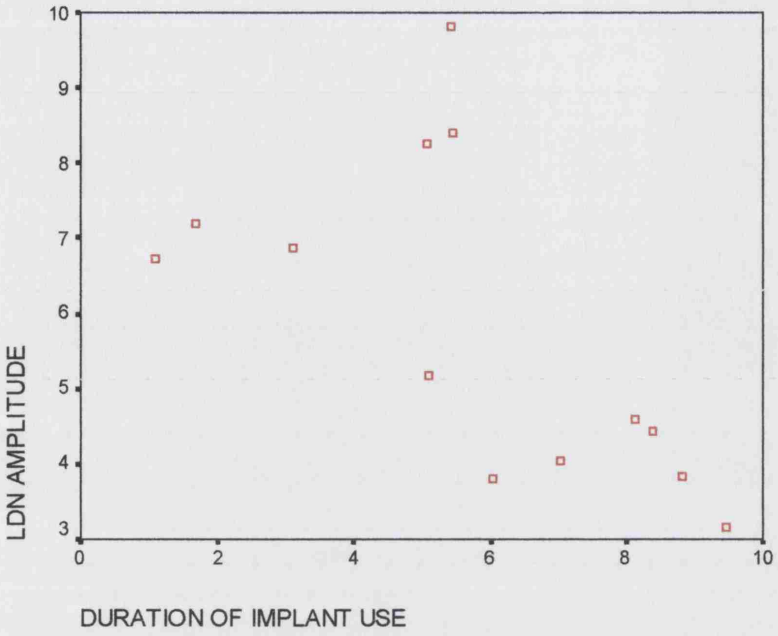

Figure 22 K: Late discriminative negativity (LDN) amplitude (μV) vs duration of implant use (years)

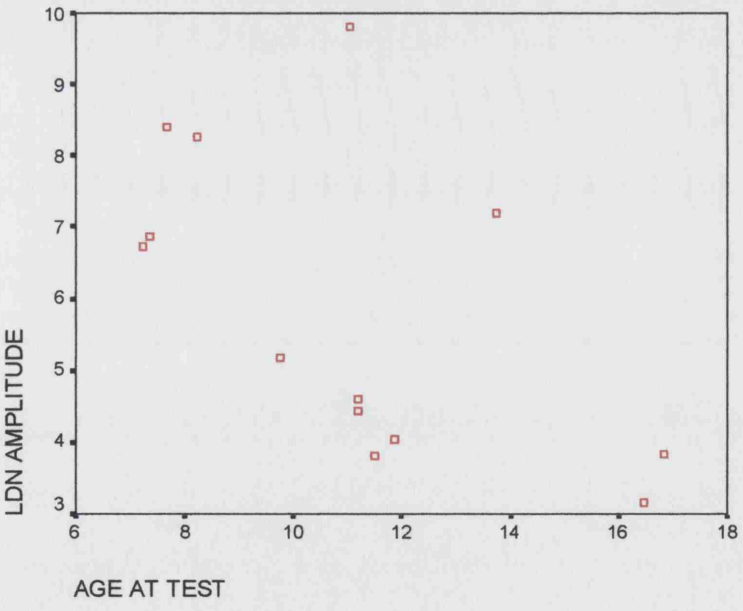

Figure 22 L: Late discriminative negativity (LDN) amplitude (μV) vs age at test (years)

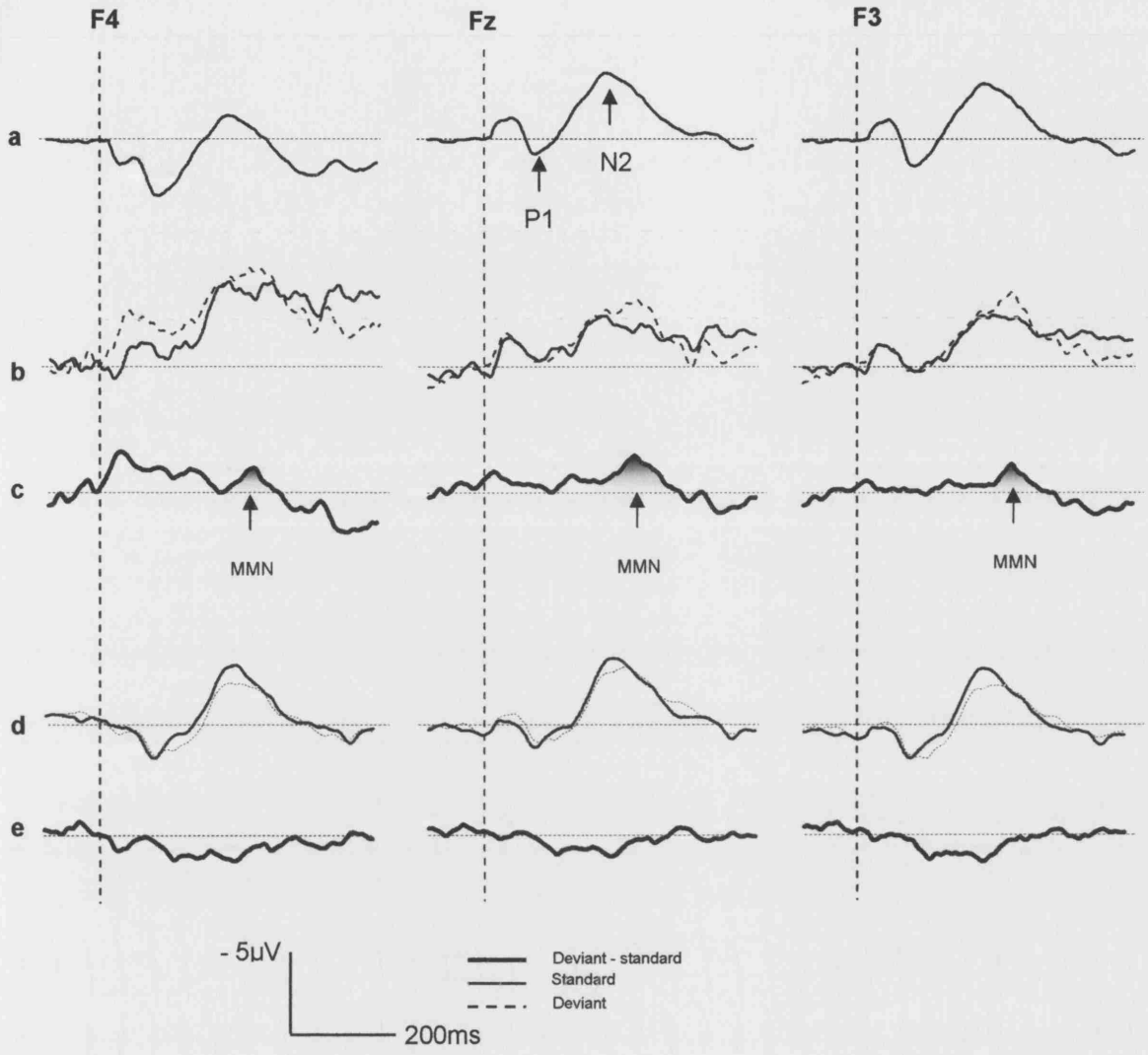

Figure 23: Grand average ERPs of cochlear implant patients recorded at F4, FZ and F3 (-100 to + 500 msec). (a) Obligatory components, P1 and N2 in all patients, (b) standards and deviants in 'star' performers, (c) Mismatch negativity (MMN) revealed by the subtraction wave form in 'star' performers 'shaded area', (d) standards and deviants in 'poor' performers, (e) subtraction wave revealing no MMN in 'poor' performers.

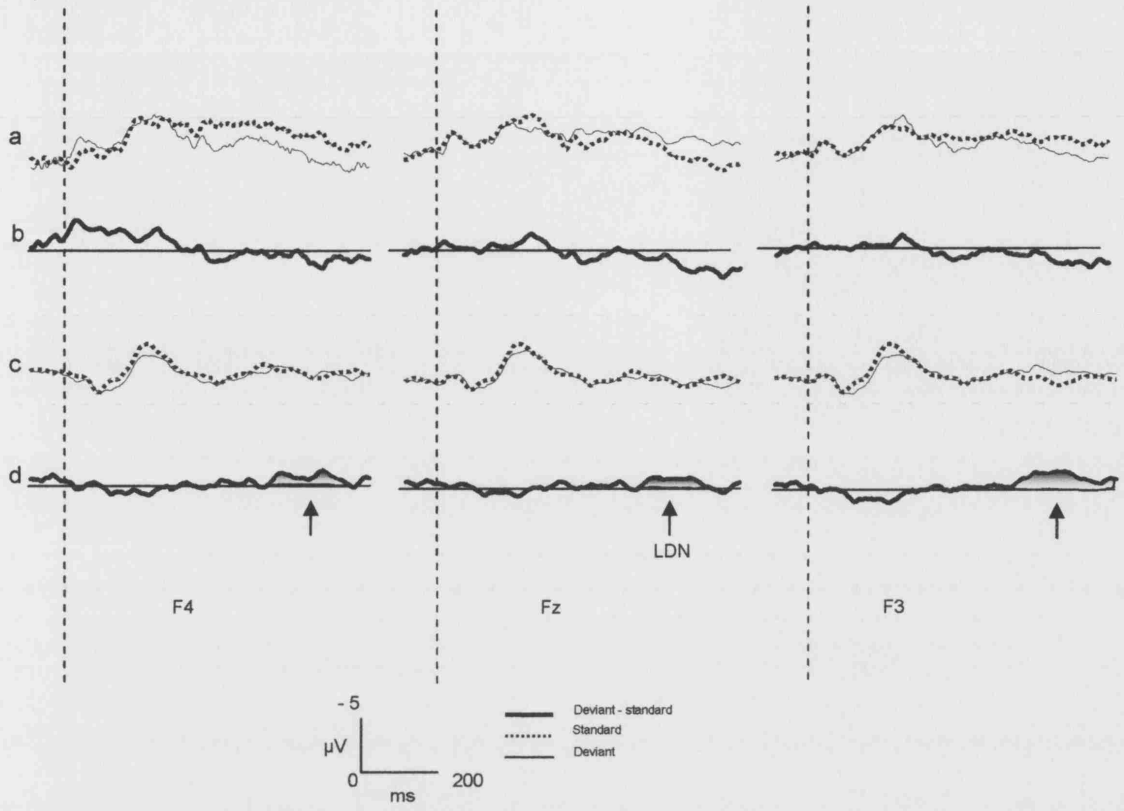

Figure 24: Grand average ERPs of cochlear implant patients recorded at F4, FZ and F3 (-100 TO +900 msec). (a) standards and deviants in 'star' performers, (b) Absent Late discriminative negativity (LDN) in the subtraction wave form of 'star' performers 'shaded area', (c) standards and deviants in 'poor' performers, (e) subtraction wave revealing LDN in 'poor' performers.

6 DISCUSSION

The investigations carried out in this thesis attempted to address the issue of identification of an objective prognostic marker for young children who have received a cochlear implant. This was carried out by investigating the correlation between electrophysiological measures such as late event related potentials and behavioural outcomes in cochlear implant children.

An observational, cross sectional, non-randomized, cohort study was conducted investigating auditory event related potentials to speech stimuli in 35 cochlear implant patients between the ages of 7 and 17 years and compared the occurrence, latencies and amplitudes of P1, N2, MMN and LDN with overall behavioural outcome in these children. Behavioural measures included category of auditory performance scores (CAP) and speech intelligibility rating scores (SIR).

A clear MMN was seen in 80-85% of 'star' performers but in only 15-20% of poor performers. Patients with higher SIR scores also demonstrated statistically significant longer duration of MMN compared to those with a lower SIR score. In pre-lingually deaf children, P1 showed a statistically significant decrease in latency with increasing duration of implant use, but not with the actual age of the patient.

The results of this study indicate that MMN can be used to assess the functional status of the auditory cortex in young children with cochlear implants and may provide an objective mechanism for differentiating good from poor performers.

6.1 SUMMARY OF SALIENT FINDINGS

The salient findings of this research are:

- Event related potentials can be recorded in cochlear implant patients by sound field stimulation using speech stimuli. Artefacts generated by the cochlear implant package and speech processor are important factors that can make recording evoked potentials in these patients, difficult.
- The main obligatory components seen in cochlear implant children are the P1 (P85-120) and N2 (N200-400)
- In pre-lingually deaf patients, the peak latency of P1 decreases with increasing duration of implant use, but not with increasing chronological age of the patient indicating its pattern of maturation with exposure to auditory stimuli by use of implant. The rate of maturation in cochlear implant children of age 7 to 17 years, using implants variably between 1 and 10 years is 3.65 ms per year.
- Both P1 and N2 components are symmetrically distributed over both hemispheres in paediatric cochlear implant patients.
- Maturation of P1 and N2 components is independent of behavioural outcome in cochlear implant children.
- MMN was demonstrated by 80-85% of 'star' performers, but only 15-20% of poor performers. Better overall behavioural performance is associated with increased probability of presence of MMN.
- Peak latency and amplitude of MMN do not correlate with behavioural outcome scores. However, duration of MMN was longer in patients with better behavioural outcome scores.
- MMN in cochlear implant patients is distributed symmetrically over both hemispheres.

- MMN parameters (latency, amplitude and duration) did not show any maturation pattern with age of the patient or duration of implant use
- A second negativity termed 'late negativity' was demonstrated in 40% of cochlear implant patients. The duration of this negativity correlated inversely with behavioural outcome scores.
- Latency, amplitude and duration measures of 'late negativity' did not show any maturational pattern with age of the patient or duration of implant use.

6.2 RECORDING OF ERPS, DURATION OF SESSION

This study demonstrates that long latency evoked potentials can be reliably recorded in cochlear implant patients using sound field speech stimuli. Thirty out of thirty-five patients demonstrated obligatory components, P1 and N2, although N1 was absent in all the subjects included in the study (See Section 5.1). Ten of the thirty-five patients demonstrated a mismatch negativity (MMN) and 14 subjects demonstrated a late discriminative negativity (LDN) although the value of detecting this waveform is yet to be proven given the fact that there is little in the literature on this topic even in normal hearing patients. Thus any useful comparisons, which may have clinical significance, cannot be defined (See Section 1.4.4.6).

Each recording required the subjects to sit quietly with minimal head movement for 4, 10 minute sessions with a break of 2 – 3 minutes between each session and one 4 minute session at the end. Prior to the recording, it took about 15 minutes to position all electrodes on the scalp. As such the total test time was 1.25 hours, through out which the subjects watched a silent movie of their choice. All the subjects in the study cooperated very well for the entire period of the recording. The older subjects aged 15

years and above reported at the end of the recording that they were slightly bored. Such complaints were not felt by the younger subjects all of whom were quite happy through out the duration of the recording.

The experiences from these 35 recordings indicate that it is perfectly feasible to record evoked potentials in young children lasting about one and quarter hours. The youngest in our study was 7 years old and she too cooperated very well for the entire duration of the recording. Playing a silent video as we did in our study was very important because:

- It kept the children entertained and prevented them from falling asleep.
- It kept their eyes focused on the screen and reduced eye movement artefacts considerably. Recordings done during breaks when the video was switched off showed a high incidence of blink and eye movement artefacts.
- Body and head movements were lesser when the subjects were interested in the video than at times when the video was switched off.

The question of feasibility of doing these recordings lasting about an hour is especially important in a clinical setting involving children. This study indicates that evoked potential studies can be carried out in children with reasonable certainty of good patient cooperation. Further, since these recordings are carried out in blocks of ten minutes, it is possible to carry out the entire recording over several sittings in those children who may be more difficult to keep inactive or in much younger children. Such practice, although involving the repositioning of scalp electrodes every time the recording is done, may produce better signal quality due to increased patient attention. It is unlikely that any recording lasting for longer than 1.25 hours would be

feasible, since the majority of the older subjects reported that they were getting restless towards the last ten minutes.

The issue of 'long duration' of recording as a limiting factor has been pointed out by several researchers in the past. Lang and co-workers have suggested a maximum duration of one hour for one session in the case of elderly and school age children while emphasising that the test session needs to be shorter in younger subjects, since MMN amplitude begins to attenuate after 1 to 2 hours of recording (Lang, Eerola et al., 1995). We did not look for the effect of duration of recording on MMN in our study. Unfortunately, this report was from unpublished data and as such could not be reviewed. Our experience indicates that the figure of less than one hour for children is slightly short. In terms of patient interest and concentration, the 7 – 10 year olds did very well for 1.25 hours. It was the group of older subjects (> 15 years age), who complained of boredom.

In conclusion, MMN and obligatory components can be recorded reliably in children between the age of 7 and 17 years in a single sitting. The use of a silent video is of paramount importance in maintaining patient interest and quality of recording.

6.3 OBLIGATORY COMPONENTS

The majority of our patients (30 out of 35) demonstrated obligatory components. Twenty nine of these patients demonstrated P1 and N2 components (Figure 25). In 1 patient, only the N2 component was recorded. A convincing N1 was not observed in any of our patients.

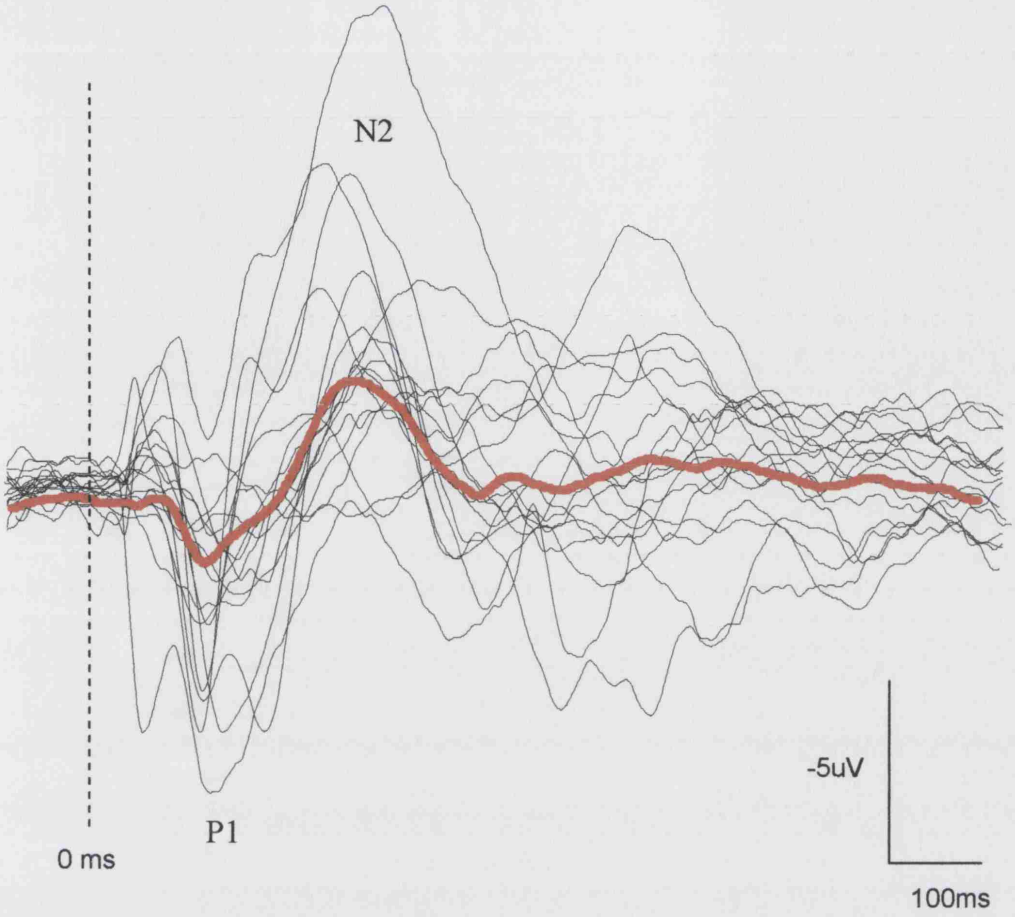

Figure 25: P1 N2 components in individual cochlear implant subjects. The red line is the grand average of all the patients

Assessment of the 5 patients who did not demonstrate any obligatory components with respect to their age, duration of implant use or aetiological profile did not reveal any commonality between them. Absence of obligatory components in these patients is difficult to explain. It is possible that the reason for not recording obligatory components is a poor signal to noise ratio in individual recordings of these patients. It may be that artefacts contaminating recordings in these patients have prevented visual identification of the individual obligatory components. However, in one of these patients who demonstrated an MMN, it is possible that subtraction wave form analysis [/da/ as standard subtracted from /da/ as deviant] removed the artefacts which

equally contaminated both the recordings, revealing the difference between the two which presented as an MMN in this patient.

The presence of P1 and N2 components and the absence of N1 are not surprising in the light of the known maturational profile of these components in normal hearing children (See Section 1.4.4.4). It might be expected that P1 and N2 components would dominate the picture until about 10 – 12 years of implant use (analogous to a normal hearing child of 10 – 12 years) and that N1 would begin to emerge at about 12 – 13 years of implant use. Since the maximum duration of implant use in pre-lingually deaf children in our study was 10 years, irrespective of the maximum chronological age of 17 years, which would not be a factor in ERP maturation in this group, we did not expect to see any N1 component in our study. This concurred with our findings.

An absent N1 in cochlear implant patients has been reported by other researchers. Ponton and co-workers (2001) reported an absent N1 to be a notable feature in ERPs recorded in cochlear implant patients (Ponton & Eggermont, 2001). Groenen et al (1996) recorded event related potentials in 7 cochlear implant patients. Their group average analysis revealed N1 in both 'good' and 'poor' performers. However, it is important to note that all subjects in their study were post-lingually deafened adults. Five of the seven subjects enjoyed normal hearing until their late 20s and 30s. Only 2 subjects lost their hearing at the age of 7 years. Their paper does not demonstrate individual recordings and as such it is not possible to confirm if the N1 was present in all patients at individual level. Based on their findings, it appears that N1 is present in post-lingually deafened cochlear implant patients, who have lost their hearing in their 20s and 30s (with the exception of two subjects; individual data was not available to review) (Groenen, Makhdoum et al., 1996).

Analysis of the wave forms of the two post lingual patients in our study also did not demonstrate any convincing N1. The age of deafness in the two post-lingual patients included in our study was 12 and 15 years. This suggests that these two patients were at the borderline with respect to emergence of the N1 component, phase cancelling the P1. It is possible that meningitis and the onset of deafness in these two children arrested the maturation of the ERPs resulting in persistence of the P1 and N2 components. The latency of P1 in one of these patients (12 years old at the time of deafness) was indeed only 66ms, similar to the expected value for a pre-lingually deaf child using a cochlear implant for 10 – 12 year. The other patient (15 years at deafness) demonstrated a P1 latency of 163 ms which does not fit in with the above model. It is possible however that in this particular patient an emerging N1 may have phase cancelled the P1 distorting its morphology giving the false impression that the latency of the P1 was at 163 ms. Further, onset of meningitis at this stage may have arrested the development of the N1 not permitting its recording at the time of our experiment.

Eggermont and co-workers carried out a longitudinal study on two children with cochlear implants (Eggermont & Ponton 2003). One of these had a Mondini deformity and had been deaf since birth. The other suffered from deafness due to meningitis at the age of 3 years. Both the children were implanted at the age of 6 years. In comparison to normal children, the latency of P1 in both these children was delayed by a period equal to their duration of deafness. However P1 latency matured at a normal rate ultimately reaching asymptote levels at about 6 – 8 years after implantation. Even after the age of 10 and 15 years, neither demonstrated any N1. Based on this, they suggested that absence or profound immaturity of N1 is an indicator of arrest or alteration of the maturation of auditory cortex. They further

suggested that there seems to be a critical period during which auditory deprivation will lead to permanent immaturity of the pathways as reflected by absence of N1 in the meningitis patient. This period is likely to be between three and six years.

Assessment of the maturational profile of P1 in pre-lingually deaf patients revealed very interesting results. P1 latency decreased with increasing duration of implant use (1 – 10 years), but not with increasing age of the patient (7 to 17 years). This decrease in latency was best described by a model assuming a linear relationship as described in section 5.1. Based on this analysis, it appears that in cochlear implant children, the latency of P1 to speech stimuli reduces by 3.65ms for every year of use of implant. This pattern of maturation of P1 with use of implant as described above suggests that during the period of deafness, some aspects of the central auditory nervous system activity do not mature completely as indicated by prolonged latencies in those who had used the implant for shorter durations. Once stimulation of the auditory pathways is restored by the use of a cochlear implant, maturation of the neural sources contributing to P1 is resumed. As a result those who had used their implant for longer duration demonstrated a reduction of their P1 latency. ERP studies looking at maturation rate of obligatory components in normal children have previously been carried out. However owing to differences in age ranges, sample sizes, recording protocols etc, there is no one figure that can define rate of maturation of these components. This is especially because obligatory components like P1 are exogenous, and therefore have varying latencies depending on the nature of stimuli and the rate of presentation of stimuli (factors exogenous to the person) (See section 1.4.4). A series of studies carried out by Ponton and co-workers between 1996 and 2001, in cochlear implanted children and normal hearing children initially indicated that the rate of maturation in cochlear implant and normal hearing group was the same but that the

cochlear implant group lagged behind the normal hearing group by the duration of deafness prior to implantation (Ponton, Don et al., 1996b; Ponton, Moore, et al., 1999; Ponton, Eggermont et al., 2000a; Ponton, Eggermont et al., 2000b). Similar results were reported by Eggermont and co-workers in cochlear implant children, implanted after an average period of deafness of 4.5 years (Eggermont, Ponton et al., 1997). They suggested that profound deafness in infants and children 'freezes' the synapses along the auditory pathway in an immature state. Restoration of neural stimulation by the action of the cochlear implant appears to thaw the system out of its frozen state after which it resumes its normal maturational time course. Later studies by Ponton et al (Ponton & Eggermont, 2001) however concluded that cochlear implant patients actually had a faster rate of maturation than the normal hearing group, although this is contradictory to the concept of delayed maturation due to sensory deprivation in the cochlear implant group. Sharma and co-workers in 2002 assessed the development of P1 response latencies in 104 congenitally deaf children who had been fit with cochlear implants at ages ranging from 1.3 to 17.5 years. They carried out a comparison of P1 latencies in implanted children with those of age-matched normal-hearing peers. Their results demonstrated that implanted children with the longest period of auditory deprivation before implantation (7 or more years) had abnormal cortical response latencies to speech. However implanted children with the shortest period of auditory deprivation (approximately 3.5 years or less) evidenced age-appropriate latency responses within 6 months after the onset of electrical stimulation (Sharma, Dorman et al., 2002). They hypothesized that central auditory pathways remain minimally degenerate after shorter periods of auditory deprivation lasting 2 – 3 years. Therefore implantation within this period may not result in lasting delays in maturation of the central auditory system. (Sharma, Dorman et al., 2002b).

Although comparison with normal hearing children is useful, one must bear in mind certain fundamental differences between the way auditory pathways may be maturing in cochlear implant and normal hearing children. Unlike normal hearing children, in whom auditory input is bilateral, the present generation of cochlear implant subjects generally have only unilateral hearing. This difference between the two groups is bound to make a difference to the transmission and synaptic delays in the peripheral auditory pathways and, therefore, the extent and rate of maturation of ERPs in the two groups. As such, it is equally, if not more valuable, to assess the absolute rate of maturation of P1 components in cochlear implant children without comparison to normal hearing children; as carried out in our study.

Since the majority of patients demonstrating the P1 component in our study were congenitally deaf, the stipulated rate of maturation (slope) is more indicative of cochlear implant children, with congenital onset. Further, given that the rate of maturation was represented best by a straight line in comparison to logarithmic or exponential models; this indicates that the rate of maturation of P1 latency does not change with increasing use of implant. Since our study did not have any patients using cochlear implants for longer than 10 years, we could not conclude the age at which this pattern of maturation would slow down or complete. We could only deduce that the maturation of P1 component was not complete at ten years since use of implant. Analysis of longitudinal data from two implanted children carried out by Ponton et al indicates that P1 latency may not decrease significantly after the age of 12. As a result P1 latency remains prolonged compared to age matched normal hearing subjects and implanted subjects with adult onset deafness (Ponton, Moore et al., 1999).

As discussed before, age at implantation is a very important prognostic predictor of outcome of implantation with children implanted early demonstrating significantly better outcomes, in comparison to those implanted late (See section 1.2.7). Electrophysiological studies demonstrating effect of age at implantation have been carried out in the past. Sharma and co-workers examined changes in the cortical auditory evoked response waveform and P1 latency in 22 pre-lingually deafened early implanted children. They found that the cortical auditory evoked response waveforms undergo rapid changes in morphology in the first 6 to 8 months after implantation. During the same period P1 latencies decrease rapidly (Sharma, Dorman et al., 2002c). They suggested that increasing periods of auditory deprivation progressively alter synaptic efficiency and transmission times causing delays in the maturation of P1 latency in those children who are implanted late.

Our study did not demonstrate any significant correlation between latency and amplitude of obligatory components (P1, N2 latency and amplitude) and age at implantation. Further detailed analysis of the maturation of obligatory components in those implanted early (< 3.5 years, n=7), middle (3.6 – 7.0 years, n=15) and late (>/=7.0 years, n=5) did not reveal any differences between the different groups as illustrated in Figure 20N. This was not in agreement with findings of Sharma and co-workers in 2002. (Sharma, Dorman et al 2002). They assessed P1 latencies in 104 children and found that two thirds of children in the middle implanted group (age of implantation: 3.6 – 7 years) and nearly all of the subjects in the late-implanted group had delayed P1 latencies in comparison to those in the early implanted group whose latencies were within the range for normal age matched children. This disparity may be due to two main reasons. Firstly, the majority of children in our study were implanted after the age of 3.5 years and as such the average of our group does not fall

in the category of 'early implanted children.' The numbers of children in the early and late groups are relatively small which may have prevented any differences in the pattern of maturation between the different groups from emerging. Secondly it is important to note, that the above study did not elaborate on the individual durations of implant use and instead compared the differences in the maturation of P1 latency in the three groups with chronological age of the patients. As is evident from our results and that from work done by other researchers (Eggermont, Ponton et al., 1997; Ponton, Don et al., 1996b), the period of auditory deprivation prior to use of implant and therefore the actual duration of implant use cannot be ignored when carrying out such investigation. Indeed our results looking at maturation of P1 latency with chronological age of patient did not demonstrate any correlation (Figure 20 H).

Bi-variate correlation analysis assessing the relationship between P1 latency and measures of behavioural outcome, namely CAP and SIR scores, demonstrated a trend of decreasing latency with increasing CAP and SIR scores, although this relationship was not statistically significant. This is explicable on the basis that these scores used in our study are indicators of general global outcome from implantation and depend not only on factors dictating the patients' neurological status such as neural plasticity, cortical damage by meningitis, developmental deficits etc, but also on extraneous factors such as attitude of patients and relatives, level of rehabilitation, motivation and confidence. P1 component of cortical evoked potentials on the other hand reflects specifically the sum of transmission and synaptic delays along peripheral and central pathways (Sharma, Dorman et al., 2002b). When applied to a clinical setting, maturation of P1 latency cannot be associated with overall improved behavioural performance. However abnormal maturation or worsening of the P1 latency can point towards poor stimulation of the auditory cortex, which may be due to a defective

device, poor patient compliance or neural dysynchrony. But before these comparisons can be drawn, normative data using standardized stimuli in cochlear implant patients needs to be established. Such data needs to be collected not only by cross sectional analysis as in our group, but also by longitudinal studies.

Examination of N2 latency and P1 N2 amplitude across age of the patients, duration of implant use and behavioural performance scores did not reveal any relationship. Very few studies have assessed these parameters in normal children and much less in cochlear implant children. As such it is difficult to explain robustly our results with regard to these parameters.

Our study demonstrated a symmetrical distribution of the P1 component across the two hemispheres in the right side implant patients. The left side implant patients were not included in this analysis due to the small number. Bilateral equal distribution of P1 is characteristic of normal hearing children (See Section 1.4.4.4).

Previous work by other researchers in cochlear implant subjects has demonstrated similar results with respect to P1. In implanted children, P1 has been found to be present over both hemispheres. (Ponton, Eggermont et al., 2000a).

6.4 MISMATCH NEGATIVITY

MMN studies carried out in healthy subjects and clinical groups clearly demonstrate that a prominent well developed stable MMN can be obtained from all normal adults and children although in the latter the amplitude and latency of MMN exhibits much wider variation and has been shown to be absent in 25 – 30 % of infants and 50 % of newborns in some studies (Cheour, Leppanen et al., 2000). MMN has a fast maturational profile and is developmentally quite stable from early childhood. (See

Section 1.4.4.5.2.2). Based on current evidence (See Section 1.4.4.5.2.), it is reasonable to conclude that MMN is an indicator of normal central auditory processing at the level of cerebral cortex. These and other attributes (See Section 1.4.4.5.2) have projected MMN as a promising tool to investigate language perception, memory and auditory discrimination in groups of children.

Based on the above, we hypothesized that cochlear implant patients who are doing very well in terms of good receptive and expressive language development may be able to demonstrate a MMN to speech stimuli. Those who are not doing well either because of inherent neurological limitations such as poor cortical plasticity or other developmental deficits or because of inadequate rehabilitation are less likely to demonstrate an MMN. Further, although MMN attributes in children have been shown to exhibit wide variability (Cheour, Alho et al., 1998; Kurtzberg, Vaughan et al., 1995; Leppanen & Lyytinen, 1997), we tried to analyze these parameters in our study to demonstrate any correlation with behavioural scores as this would help in quantifying any effect observed.

Speech stimuli have been used previously to elicit MMN in cochlear implant patients. Kraus and co-workers were one of the first to evaluate MMN in nine post-lingual, adult, cochlear implant patients using speech stimuli /da/ and /ta/. Eight of these subjects who were good users demonstrated an MMN, whereas one of these subjects who was a poor user did not. Interestingly this poor user did demonstrate an MMN when a different stimulus pair /da/ and /di/ was used. The spectral components of /da/ and /di/ are very different from each other and as such are processed more distinctly by the 22 channel implant system used by this patient. They concluded than MMN was a promising measure for the objective evaluation of cochlear implant function.

(Kraus, Micco et al., 1993). Groenen and co-workers used similar stimuli (/ba/ and /da/) to record MMN in 3 'good' cochlear implant users and 4 'poor' cochlear implant users, categorized on the basis of their performance in monosyllable, spondee and short vowel identification tests (Groenen, Snik et al., 1996). All the subjects were post-lingually deafened adults. Group average analysis of the good performers revealed an MMN, whereas that of the poor performers did not. Individual analysis revealed absent MMN in one of the three 'good' performers and all the 'poor' performers. Based on these results, they proposed that electrophysiological studies can be used to monitor the neurophysiological function of cochlear implant subjects. The main limitation of their study was the small number of subjects. Although the study was carried out in adult patients, their results did point at the potential use of electrophysiological tests in children especially pre-lingually and congenitally deaf children who are much more susceptible to immature auditory cortical function and cannot perform behavioural tests reliably. Kileny and co-workers in 1997 investigated MMN and P 300 in 14 cochlear implanted children, between the ages of 4 and 12 years, using differences in intensity and tone of stimuli and also using differences in speech stimuli (Kileny, Boerst et al., 1997). They studied the relationship between amplitude and latency of the cognitive responses namely N1, P2, N2 and P3 and MMN and speech recognition abilities. One of the main findings of their study was that all evoked potential components including P300 and MMN were identifiable in most subjects although the N1 component was identified least often. The latencies of most components was affected by stimulus type. It tended to be shorter for the frequency contrast than for the loudness contrast, which in turn tended to be shorter than for the speech contrast, although these differences were not statistically significant. They suggested that this may be a reflection of the increased processing

time required for the speech stimuli because of its higher complexity. In frequency, the discrimination showed shorter and stronger P3 and MMN that were associated with high sentence recognition scores. Based on this relationship between MMN and speech recognition scores, they concluded that MMN and P 300 hold promise as a clinically useful technique for evaluating young children with cochlear implants.

Wable and co-workers in 2000 investigated MMN using electrical stimuli in 8 adult cochlear implant subjects, aged 40 – 71 years, who had been post-lingually deaf from 1 to 13 years and implanted for 3 – 36 months and compared the results with their speech performance. A Classical P1- N1- P2 wave was identified in 6 out of these 8 subjects. No relationship between MMN and speech performance was found. They suggested that this might be due to the small number of patients (Wable, van Den et al., 2000).

Ten out of thirty-five patients in our study demonstrated a MMN. The aetiological profile of these patients is detailed in Table XI.

AETIOLOGY	TOTAL	MMN	%
Acquired			
Post-lingual meningitis	2	2	100
Pre-lingual Meningitis	3	2	66
Rubella	1	1	50
CMV	1	0	
Hypoxia at birth	2	0	0
Congenital			
Autosomal Recessive	10	2	20
Syndromes - Ushers, Wardenburgs	5	1	20
Unknown	11	2	18

Table XI: Aetiological profile of patients demonstrating MMN

It is interesting to note that both the post-lingually deafened children in our group demonstrated an MMN (100%). 66 % of patients who suffered from acquired deafness, due to meningitis in the pre-lingual age group, also demonstrated this wave. In comparison to these two groups, 50 % of patients with acquired infections and only 20 % of patients with congenital deafness (autosomal recessive or syndromic) demonstrated a convincing MMN. When split into different groups based on aetiology (Table III, XI), the small numbers of patients in each group did not allow any statistical tests to be carried out to assess if there were any differences in the evoked potential results between the different groups. However, this pattern of occurrence of MMN, with a predilection towards those who acquired deafness as compared to those who inherited it, suggests that MMN is more likely to be demonstrated by those subjects, who at some point in their life have been exposed to normal sounds, even if this may be in the uterus before birth.

The chi square analysis and the exact Fischer test results indicate that MMN is much more likely to be present in those patients who have better behavioural performance scores, as judged by CAP and SIR. In comparison to 80 – 85 % of 'star' performers demonstrating the MMN, only 16 - 20 % of 'poor' performers demonstrated an MMN. This is in agreement with our original hypothesis that 'star' performers are more likely to demonstrate the MMN, in comparison to the poor performers.

The question as to why some of the star performers do not demonstrate the wave and some poor performers do remain unanswered. With regard to 'star' performers, only 1 patient in this category on the basis of CAP or SIR score did not demonstrate an MMN. Detailed analysis of this individual's wave forms did reveal a negatively

directed component in the subtraction wave form. However since this negative component did not rise above the base line, it did not meet our criterion for a MMN.

With regard to poor performers, 4 out 28 (based on CAP Scores) and 6 out of 30 (based on SIR Scores) poor performing patients demonstrated an MMN. Presence of MMN in those patients who were poor performers based on behavioural assessment scores can be explained as follows. These patients may progress on to achieving higher CAP and SIR scores with time, since they may have acquired good auditory memory and discrimination as indicated by the presence of MMN. The reason for their poor behavioural score may lie in other factors such as duration of implant use, coexisting medical conditions and nature of rehabilitation. In one of these children, who demonstrated a good MMN, the development of expressive and receptive language was significantly limited by the nature of his rehabilitation, which was based primarily on sign language since the subjects' teacher was a deaf signer herself. Further investigation into the possible reasons for poor performance in three children who were implanted early revealed interesting facts. Two of these were congenitally deaf and syndromic (Ushers, Waardenburg). Both these children were implanted before 3.5 years of age with complete insertion and activation of all electrodes. In one of them the implant was not effectively used in the first few months after implantation due to social reasons. This may partly explain the reason for poor progress inspite of early implantation in this child. The other child enjoyed satisfactory input in terms of training and rehabilitation from the very beginning. Neither of them achieved optimal results even 5 – 7 years after implantation. Evoked potential wave forms of these children demonstrated normal P1 for their duration of implant use but absent MMN. It may be that complete absence of any auditory input at any time prior to implantation in these syndromic children suggests that the auditory cortex was not able to mature

beyond a certain level. As such although they are demonstrating obligatory wave forms at the cortical level, they are not able to process complex speech sounds enough to generate a MMN with the speech stimuli used in our study. It is possible that less complex speech stimuli may elicit a MMN in these patients suggesting that they are able to cope with sounds up to a certain level of complexity. Absence of MMN with any stimuli in these patients may suggest that they are unlikely to do well with implants alone and might need more support in the form of sign language. Another of the three children who was implanted early and received a full insertion of cochlear implant, did not do well in terms of his behavioural performance measured by CAP and SIR scores in distinction to what might have been expected based on his age of implantation. No obvious reason could be identified for his poor performance. He too demonstrated a normal P1 for his duration of implant use suggesting that the implant was providing him with some level of auditory input. The reason for his poor performance may lie in limitation in the central processing abilities of his auditory cortex as suggested by absent MMN. Serial recordings of evoked potential response to these and simpler stimuli needs to be carried out to ascertain if MMN is present or appears in future as this would point towards potential improvement in his behavioural performance. Absent MMN to any stimuli may indicate lack of any potential of developing good speech and language. It needs to be stressed however that these assumptions need to be verified in a larger longitudinal study.

Given that MMN is an indicator of normal auditory sensory memory and auditory discrimination, which are prerequisites for normal central auditory processing, if used as a clinical test, the above figures would suggest a sensitivity and specificity of 80 - 85% in detecting good central processing skills objectively, using MMN in cochlear implant patients (Table XII). Given the fact that recording MMN is a completely safe

non-invasive procedure, the above figures are supportive of its use as a potential clinical tool in cochlear implant patients to shed more light on the central processing function of some patients, who are borderline in their behavioural performance or in those patients in whom behavioural tests cannot be carried out. However keeping in mind the cross sectional design of this study and relatively small number of star performers, a much larger longitudinal study is required to prove / refute the prognostic power of MMN in cochlear implant patients. Should such a longitudinal study indicate a positive correlation between occurrence of MMN and good behavioural outcome, MMN may become a useful clinical test predicting prognosis in young cochlear implant patients.

	CAP SCORE		SIR SCORE	
	7	<=5	6	<=3
Total patients	7	21	5	19
MMN +	6	4	4	3
MMN -	1	17	1	16
Sensitivity	85.71%		80.00%	
Specificity		80.95%		84.21%

Table XII: Sensitivity and specificity of MMN recorded at Fz, as a clinical test identifying good central auditory function based on CAP / SIR scores.

Numbers of star and poor performers were very similar between the two methods of behavioural assessments used in our study. As such the sensitivity and specificity of MMN as a potential clinical test was comparable between CAP and SIR scores. Only one patient in the 'star' performer category based on CAP score had a poor SIR score. As discussed before (See section 3.3.6) both these methods of assessment are reliable and repeatable. However they do reflect slightly different aspects of hearing, speech and language with CAP scores primarily being indicative of auditory perception and SIR score primarily indicating the individuals' expressive language abilities. The biological processes involved in the interaction between these two aspects in any one individual is complex and multifactorial. As such we have not attempted to explain this slight apparent disparity in the results of assessment in this one patient.

Our study did not find any relationship between MMN parameters and chronological age of the patient, duration of implant use or age at implantation. This is not surprising given that auditory memory and discrimination, both of which are prerequisites for MMN to be elicited are present in normal children much before development of any language. As such one would expect MMN to evolve soon after implantation and have a fast maturation curve. Based on work done by other researchers, there is reasonable evidence to believe that MMN in normal hearing children may be 'adult like' at a very early age (See Section 1.4.4.5.2.2). Based on the work by Csepe and co-workers and Cheour et al in 1995, it seems that the maturation age of MMN is at the same time as that for P2 (Cheour-Luhtanen, Alho et al., 1995; Csepe, 1995). The maturation for P2 has been equated with that of Auditory Brain Stem responses, becoming adult like at the age of two years (Eggermont, 1988). One can therefore argue that in the case of those children who lost their hearing after two years of normal hearing, the maturation of MMN should be normal and independent

of the age at implantation. Also, in congenitally deaf children who receive a cochlear implant, in the absence of any other pathology that may have affected the maturation or plasticity of the auditory cortex, it should be possible to record MMN two years after implantation. This suggests that the majority of patients who demonstrate an MMN would have done so 2 years after implantation if tested at that time. Although our study does not prove this evolution since we did not perform any serial recordings of MMN, if true, as derived from the maturation pattern of MMN, carrying out the test two years after implantation would have a predictive value in assessing future prognosis after implantation.

Investigation of the symmetry of distribution of MMN was carried out at group level looking at the asymmetry in all the patients together since we felt that individual variation would not provide any useful inference given the small number of patients and high variability in MMN data. The analysis revealed MMN to be equally distributed over both hemispheres. This finding is very interesting since normal children demonstrate significant asymmetry with a predilection for the contra lateral side and emergence of MMN on the ipsilateral side only at the age of 8 years. (See Section 1.4.4.5.2). Although in normal children this phenomenon of asymmetry at earlier ages has been explained on the basis of maturation of the intercortical pathways with passing age, it is difficult to describe why cochlear implant children should demonstrate MMN on the ipsilateral side from the beginning. Interestingly this finding in cochlear implant patients has been reported by other researchers as well, although no satisfactory explanation has been attributed to the phenomenon (Ponton, Eggermont et al., 2000a). It is possible that in reality there does exist a pattern of maturation in cochlear implant children as seen in normal children with a shift in the distribution of MMN from the contralateral side to both sides. However

combining the data in our study across all age groups may have smeared the results creating this false impression of equal distribution of MMN over both hemispheres.

Having established that MMN was evident in 'star' performers and some average performers, we further attempted to quantify the MMN measurement.

Bi-variate correlation analysis assessing MMN parameters with behavioural outcome results revealed a positive correlation between MMN duration and SIR score but not CAP score. No such relationship was observed for MMN peak latency, area and peak amplitude with either CAP or SIR score. This was not surprising in light of the fact that MMN parameters are known to be quite variable at individual level (See Section 1.4.4.5.2) and the small number of patients demonstrating MMN in our study. Detailed analysis of the relationship between MMN duration and SIR score revealed a statistically significant relationship best described by a linear model (See Section 5.2). These results are suggestive of the fact that MMN duration is indicative of the level of behavioural outcome and therefore cortical maturation in cochlear implant patients. A longer duration of MMN is an objective indicator of better behavioural results. Whilst this fact may not seem very interesting in our subjects in whom we have both electrophysiological and behavioural results, it would be very valuable, when carrying out MMN studies in very young cochlear implant patients or those with complex problems, in whom behavioural analysis is difficult. Presence of MMN in these patients may indicate favourable prognosis in the long run since the likelihood of recording MMN is much lower in those patients who do not achieve good behavioural outcome. However this conclusion can only be drawn if the results of our study are reproduced in a larger longitudinal study.

6.5 OBJECTIVITY – RECORDING METHOD AND INTERPRETATION

The clinical application of MMN so far has been limited to a great extent by the lack of an objective detection method that can be applied to a single subject. Our study indicates that duration of MMN, which is derived from the offset and onset latency of MMN is a useful measure for assessing the magnitude of MMN. This is in partial agreement with the results of McGee and co-workers who demonstrated that latency criterion were best in objective identification and assessment of MMN (McGee, Kraus et al., 1997). However they also emphasised the importance of area under the MMN curve which is a measure of amplitude and duration. We did not find area to correlate with behavioural results of our patients.

6.6 LATE DISCRIMINATIVE NEGATIVITY

Late discriminative negativity is a relatively recent discovery (See section 1.4.4.6). There are only few studies which have reported LDN in normal children and adults. Regarding its maturation, these studies point towards decreasing latency with age and lower amplitude in adults compared to children. However this evidence is still inadequate to conclusively determine the maturational pattern of LDN. No studies until now have reported LDN in cochlear implant patients.

In comparison to findings of other researchers who reported the peak latency of LDN to be 400-450 ms, peak latency in our recordings (701 ms) is substantially delayed. It is possible that the latency of LDN in cochlear implant patients is more delayed compared to the normal population and that training and rehabilitation decrease the latency although our study did not demonstrate any such pattern. It is also possible that the late negative wave we are reporting is not the same as the conventionally reported LDN in normal patients. Lack of any maturational pattern with age or use of

implant casts doubts of this nature. However, maturation of peak latency with increased duration of implant has also not been described for other endogenous potentials like MMN. This may be due to limited number of recordings, but may also be accounted by the possibility that maturation of endogenous potentials depends far more on extent of effective training and rehabilitation and therefore performance, which in turn depends on plasticity of the auditory cortex than merely age or duration of implant use.

Analysis of the duration of LDN revealed a statistically significant negative linear relationship with both CAP and SIR score. Based on our results, one can suggest that cochlear implant patients generate a large LDN soon after cochlear implantation and with passage of time, as they acquire good discriminative skills, the magnitude of the LDN decreases. However given the meagre number of reports yet with no previous reports in cochlear implant patients, such a claim may seem premature. The main reason for reporting LDN in our study would be to contribute towards normative data in the cochlear implant group to compare it with future research work in this area.

6.7 PROPOSED FUTURE STUDIES

The results of this study clearly underline the potential value of Mismatch Negativity as a prognostic marker in children with cochlear implants. We propose to carry out a longitudinal study recording event related potentials such as P1, N2 and MMN in cochlear implant patients from 'switch on' until they develop good speech and language. This would help in collecting normative data for these potentials in cochlear implant children which may eventually establish these potentials as clinically useful tools in this group

Further research using different stimuli such as paradigms with more obvious differences like frequency discrimination using pure tones, or paradigms with more subtle differences like duration differences or different speech stimuli than the ones used in this study will allow comparisons between results obtained with these stimuli. This will help establish more specific stimulus paradigms for different population groups. Also MMN can be elicited to changes in visual stimuli and these findings can be compared with MMN due to auditory stimuli. Research using combination of stimuli as above will further add to the understanding of biological mechanisms involving neural plasticity in our brain that are responsible for adaptation using alternative senses such as lip-reading in deaf patients and reversal of these changes after rehabilitation, as occurs during relearning of oral language after cochlear implantation. .

Mismatch negativity can also be used to assess current and new programming strategies for speech processors in cochlear implanted children. Presence of MMN with one strategy over another will provide objective evidence of better signal processing especially in young children who are not able to cooperate with behavioural tests and where there is concern about progress after implantation.

7 APPENDICES

7.1 PUBLICATIONS ARISING FROM THESIS

1. Singh S, Liasis A, Rajput K, Luxon LM (2004). Short report: Methodological considerations in recording mismatch negativity in cochlear implant patients. Cochlear Implants International, 5 (2), 76 – 80.

(See section 7.1.1 for reprint of article)

2. Singh S, Liasis A, Rajput K, Luxon LM (2004). Event related potentials in cochlear implant patients. Ear and Hearing; 25 (6), 598 – 610

(See section 7.1.2 for reprint of article)

3. Singh S, Rajput K, Liasis A, Luxon LM (2004). An objective marker of auditory processing in cochlear implant patients. In preparation for submission to British Medical Journal.

4. Singh S, Rajput K, Liasis A, Luxon LM (2004). Electrophysiological tests in cochlear implant patients – a review. In preparation for submission to International Journal of Audiology.

7.1.1 Reprint of publication in Cochlear Implants International (2004). 5(2),76-80.

7.2 PRESENTATIONS ARISING FROM THESIS

1. Singh S, Rajput K, Liasis A, Luxon LM: Mismatch negativity in paediatric cochlear implant patients. 3rd meeting of British Society of Neurotology, London, September 2003

2. Singh S, Rajput K, Liasis A, Luxon LM: Mismatch negativity in paediatric cochlear implant patients. Annual conference of the British Society of Audiology, Harrogate, September 2003

3. Singh S, Rajput K, Liasis A, Wheeler A, Luxon LM: Correlation of electrophysiological measures of auditory processing with outcome in paediatric cochlear implant patients. British Cochlear Implant Group meeting, Institute of Child Health, London, September 2003

4. Singh S, Rajput K, Liasis, Luxon LM: Correlation of electrophysiological measures of auditory processing with outcome in paediatric cochlear implant patients. Royal Society of Medicine, London, May 2003

5. Singh S, Liasis A, Rajput K, Luxon LM: Correlation of electrophysiological measures of auditory processing with outcome in paediatric cochlear implant patients. CAPD Meeting, Institute of Child Health, London, April 2003

6. Singh S, Liasis A, Rajput K, Luxon LM: Methodological considerations in recording MMN in cochlear implant patients (POSTER). Third international workshop on mismatch negativity and auditory functions and dysfunctions, Lyon, France, May 2003

7.3 INFORMATION SHEETS

INFORMATION SHEET FOR PARENTS

CORRELATION OF ELECTROPHYSIOLOGICAL MEASURES OF AUDITORY PROCESSING WITH OUTCOME, IN PAEDIATRIC COCHLEAR IMPLANT PATIENTS.

We are doing a research project at the GOSH Cochlear Implant centre for which we request your permission.

Aim

The aim of this project is to try and find newer ways of identifying factors, which may affect the functioning of your child's cochlear implant successfully.

Why is the study being done?

The study is being done because we want find out why some children find it easier to use a cochlear implant than other children.

How is the study to be done?

We aim to do this by analysing the signals that your child's brain will generate when the Cochlear Implant is stimulated by our computer. The process is completely safe and will require you to sit patiently with your child for about 1 hour. We will attach about 32 electrodes to your child's fore head, scalp and behind the ear and then attach our computer to the cochlear implant. We will then send some signals through this connection and via speakers, which your child may perceive as sound. The electrodes will pick up the signals, which we will analyse later.

What are the risks and discomfort?

The procedure will not cause any discomfort or pain at all. We will only want your child to relax in a chair but not go to sleep.

What are the potential benefits?

Results from these tests may help in improving rehabilitation methods to help the child manage with the cochlear implant.

Who will have access to the case/research records?

The results will be kept confidential and will only be accessible by the researchers involved in the study.

The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact the Data Protection officer via the switchboard on 020 7405 9200 extension 5217.

What are the arrangements for compensation, should any harm come to the subject?

This project has been approved by an independent research ethics committee who believe that it is of minimal risk to you. However, research can carry unforeseen risks

and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.
No special compensation arrangements have been made for this project but you have the right to claim damages in a court of law. This would require you to prove fault on the part of the Hospital and/or any manufacturer involved.

Do I have to take part in the study?

If you decide now or at a later stage that you do not want to take part in this study, that is entirely your right and will in no way prejudice any future care your child may require.

Who do I speak to if problems arise?

If you have any complaints about the way in which this research study has been, or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact the chairman of the Research Ethics Committee, by post via the Research and Development Office, the Institute of Child Health, 30 Guilford Street, London WC1N 1EH, or if urgent by telephone on 020 72429789 ex 2620 and the committee administration will put you in contact with him.

Who do I contact if I want to know more?

If you have any more questions we will be most happy to answer. You can direct these to any one of us.

Yours truly

Dr. S Singh
Research Fellow
Academic Audiology and Cochlear Implant
Great Ormond Street Hospital for Children,
London, WC1N3JH
Tel: 020 78138107, E mail:

Professor Linda M Luxon
Academic Unit of Audiological Medicine
Institute of Child Health
30 Guildford Street
London WC1N 1EH
Tel: 020 78138107

Dr. Kaukab Rajput
Department of Cochlear Implant
Great Ormond Street Hospital for Children
Great Ormond Street
London WC1N 3JH
Tel: 020 78138316

INFORMATION SHEET FOR PATIENTS

CORRELATION OF ELECTROPHYSIOLOGICAL MEASURES OF AUDITORY PROCESSING WITH OUTCOME, IN PAEDIATRIC COCHLEAR IMPLANT PATIENTS.

We are doing some work at the GOSH Cochlear Implant centre to try to find out why some children can use a cochlear implant more easily than other children. We would like to ask you to take part in this study.

Aim

The aim of this project is to try and find why some children are not able to use the cochlear implant as well as other children.

Why is the study being done?

The study is being done because we want to find out why some children find it easier to use a cochlear implant than other children.

How is the study to be done?

We aim to do this by looking at the electric waves that your brain generates when your cochlear implant is stimulated by some special kind of sounds and signals. The process is completely safe and will need you to sit quietly watching a silent television programme with subtitles, for about 1 hour. We will attach a few electrodes (special wires) to your head and use these to record the brain waves.

What are the risks and discomfort?

The procedure will not cause any discomfort or pain at all. We will only want you to relax in a chair but not go to sleep.

What are the potential benefits?

Results from these tests may help us in giving you more specific advice to help you use your cochlear implant better.

Who will have access to the case/research records?

The results will be kept confidential and will only be seen by the researchers involved in the study. No one else will be allowed to see these test results without your permission.

Do I have to take part in the study?

If you decide now or at a later stage that you do not want to take part in this study, that is quite all right and will not make any difference to the way in which we look after you.

Who do I speak to if problems arise?

If you have any worries about this research study please speak to Dr. S Singh or Dr K Rajput or Professor Linda Luxon (contact details listed below). Your parents / carer can speak to the hospital staff and managers if necessary. If the problems are not resolved, or you wish to comment in any other way, please contact the chairman of the Research Ethics Committee, by post via the Research and Development Office, the Institute of Child Health, 30 Guilford Street, London WC1N 1EH, or if urgent by

telephone on 020 72429789 ex 2620 and the committee administration will put you in contact with him.

Who do I contact if I want to know more?

If you have any more questions we will be most happy to answer. You can direct these any one of us.

Yours truly,

Dr. S Singh
Research Fellow
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Dr. Kaukab Rajput
Department of Cochlear Implant
Great Ormond Street Hospital for Children
Great Ormond Street
London WC1N 3JH
Tel: 020 78138316

INFORMATION SHEET FOR GP

Dear Doctor,

We are writing to inform you about a research project that is being undertaken at the Great Ormond Street hospital at London which involves one of your patients who has undergone Cochlear Implantation under our care:

The title of this project is:

CORRELATION OF ELECTROPHYSIOLOGICAL MEASURES OF AUDITORY PROCESSING WITH OUTCOME, IN PAEDIATRIC COCHLEAR IMPLANT PATIENTS.

The project involves performing certain electrophysiological tests to record evoked response potentials from these patients and then comparing the findings with the final clinical outcome. We will aim to do this test mostly during the patient's routine follow up visit to the hospital.

If you have any queries, please do not hesitate to contact us.

Dr. S Singh
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Dr. Kaukab Rajput
Department of Cochlear Implant
Great Ormond Street Hospital for Children
Great Ormond Street
London WC1N 3JH
Tel: 020 78138316

7.4 DISTRIBUTION OF DATA

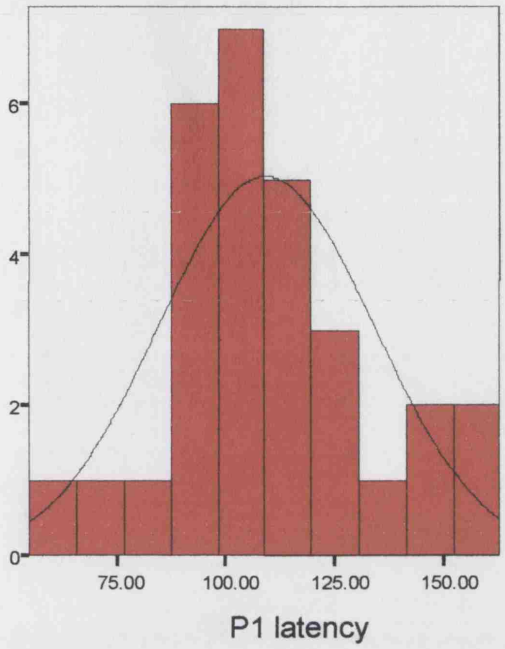

Figure 25 A: Distribution of P1 peak latency (ms)

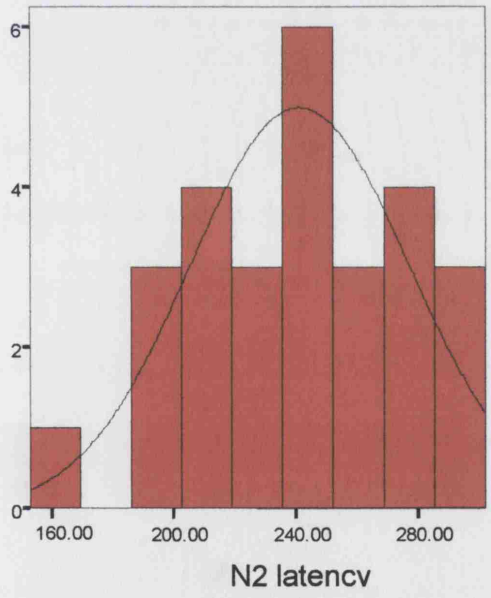

Figure 25 B: Distribution of N2 peak latency (ms)

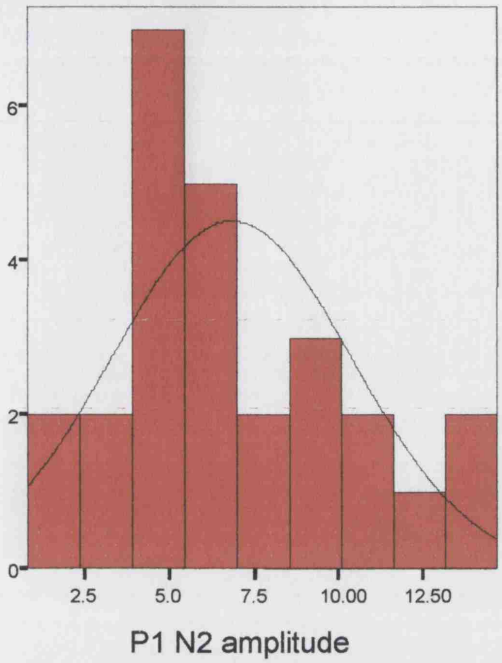

Figure 25 C: Distribution of P1 N2 amplitude (μV)

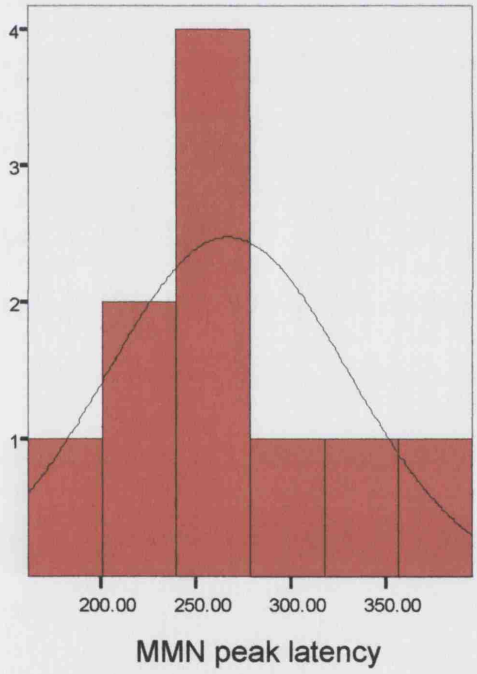

Figure 26 A: Distribution of Mismatch negativity (MMN) peak latency (ms)

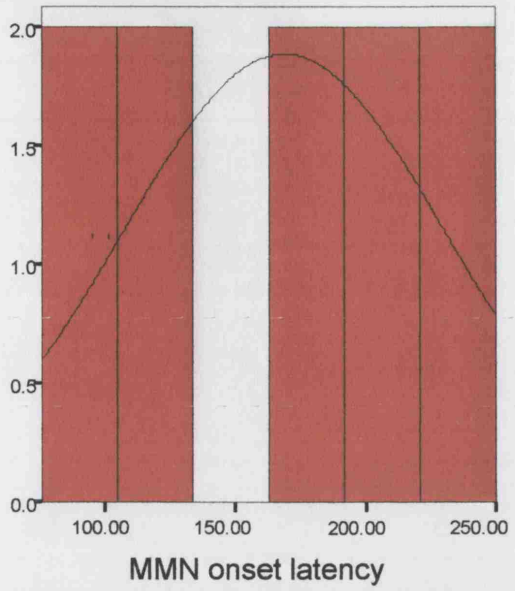

Figure 26 B: Distribution of Mismatch negativity (MMN) onset latency (ms)

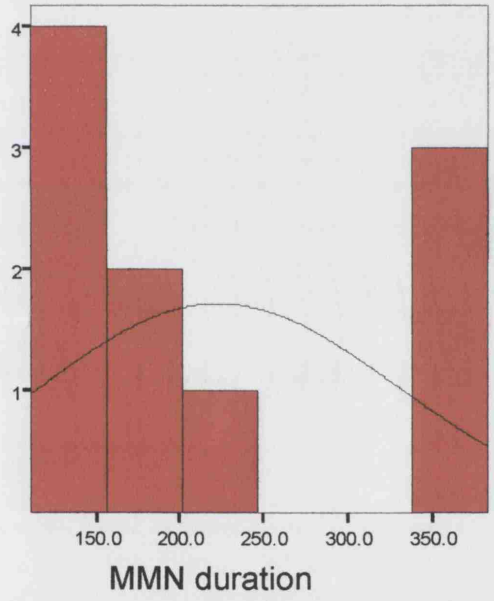

Figure 26 C: Distribution of Mismatch negativity (MMN) duration (ms)

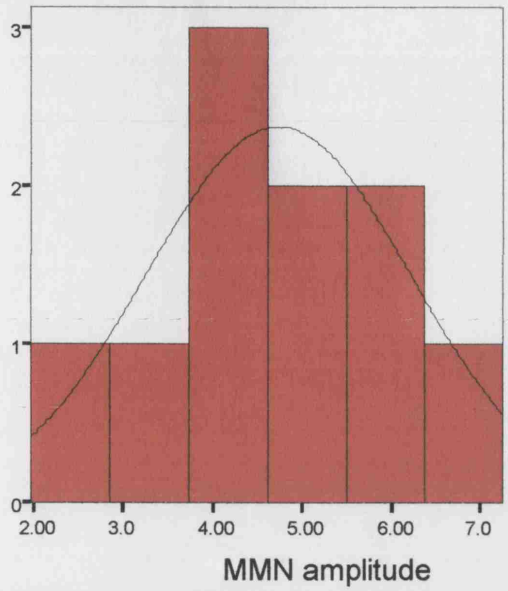

Figure 26 D: Distribution of Mismatch negativity (MMN) amplitude (peak to peak)(μV)

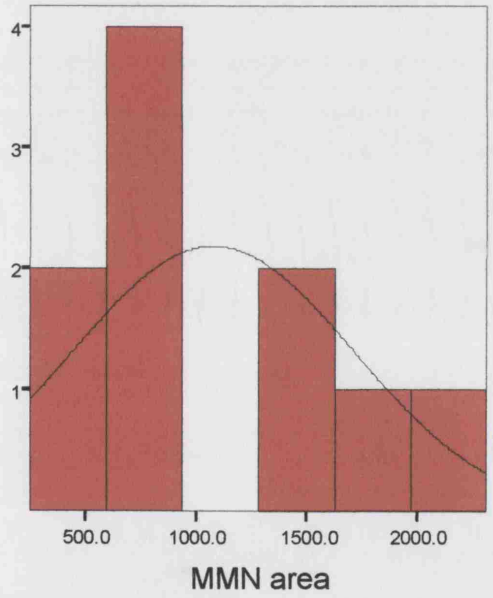

Figure 26 E: Distribution of Mismatch negativity (MMN) area (duration X amplitude)

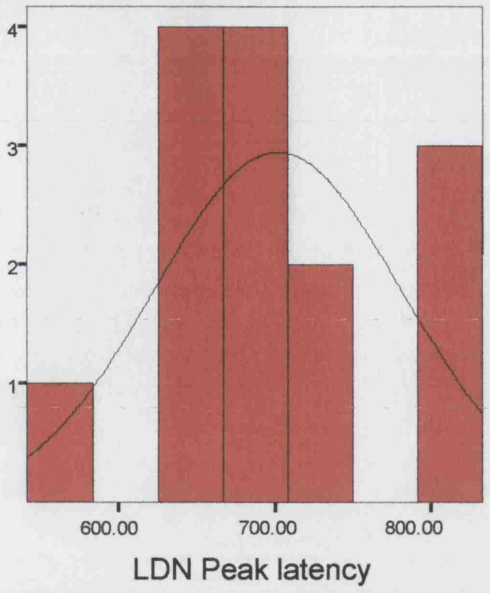

Figure 27 A: Distribution of Late discriminative negativity (LDN) peak latency (ms)

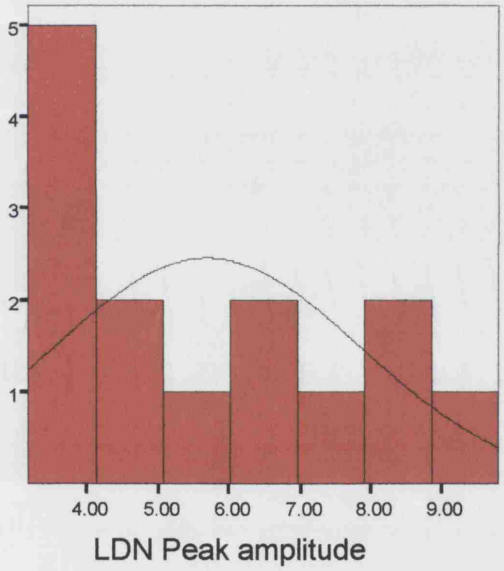

Figure 27 B: Distribution of Late discriminative negativity (LDN) peak to peak amplitude (μV)

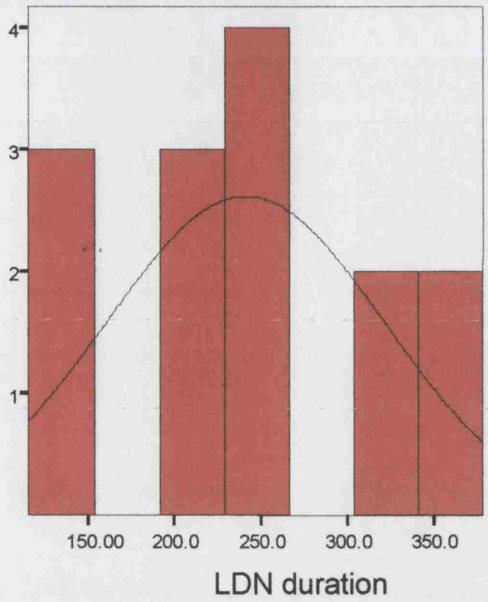

Figure 27 C: Distribution of Late discriminative negativity (LDN) duration (ms)

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